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CARCINOMA OF THE LUNG

Necessity for Exploratory Thoracotomy after Negative Bronchoscopy

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BUFFALO, NEW YORK

IN a suspected case of carcinoma of the lung, after x-ray examination, the first diagnostic tool that is usually employed is bronchoscopy. After a negative bronchoscopic report, the physician too often dismisses carcinoma as a diagnosis. A careful survey of the literature on thoracic surgery should serve to correct this assumption, and should focus attention on the limited value of bronchoscopy in diagnosis. It will also perhaps provide an idea of the prognostic significance of the negative bronchoscopic finding.

With the more frequent use of bronchoscopy, and the apparent increase in the incidence of bronchogenic carcinoma, the incidence of positive bronchoscopic findings is less than had been reported previously[1-8] (Table 1). On personal review of a group of 69 cases of carcinoma at Bellevue Hospital in which bronchoscopic examination was performed, there was indirect evidence of tumor in 17 per cent, and a tumor was seen and biopsied in 38 per cent. This is a total of 49 per cent showing some evidence of carcinoma. Biopsy was positive in only 22 per cent, however. In other words, less than 50 per cent of cases can be expected to have a positive bronchoscopy.

TABLE 1. *Bronchoscopy in Carcinoma of the Lung.*

AUTHOR	POSITIVE BRONCHOSCOPIES
	%
Lindskog[4]	28
Gibbon et al.[3]	44
Ochsner et al.[5]	38
Johnson et al.[6]	50
Brewer et al.[7]	45
Grow et al.[8]	43
Watson et al.[9]	37
Clerf and Herbut[10]	39

Cytologic study of either sputum or bronchial washings may be a very helpful adjunct in early diagnosis. The success is based on the experience of the cytologist reading the slides, and given an experienced examiner, the percentage of proved positive diagnoses is quite high (Table 2).[2, 6, 7, 9, 10]

In cases with negative bronchoscopic findings, differential diagnosis may be difficult. Three main types of lesions may be considered; the peripheral circumscribed, or mass lesion; the lobar or segmental opaque lesion, which is presumably due to bronchial obstruction; and the cavitary lesion.

TABLE 2. *Cytology of Sputum and Bronchial Washings.*

AUTHOR	POSITIVE TEST
	%
Gibbon et al.[3] (Philadelphia)	89
Strieder[9] (Boston)	85
Woolner and McDonald[10] (Mayo Clinic)	95
Watson et al.[9] (Memorial Hospital, New York City)	60

A peripheral mass may be a primary malignant, a metastatic or a benign lesion such as "tuberculoma," adenoma, hamartoma or bronchogenic cyst. In a series of 53 cases, undiagnosed preoperatively, Johnson, Clagett and Good[2] reported that 74 per cent were found to be malignant. In 24 similar cases, Blades[11] found 17 per cent malignant lesions and 30 per cent tuberculomas. In 86 cases, Grow et al.[8] found 23 per cent to be malignant. Resection is the treatment of choice for both the malignant and the benign lesions; therefore, early exploration is indicated, despite the absence of a positive preoperative diagnosis.

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Case Reports

Case 1 (Fig. 1 *A* and *B*). A 65-year-old Negro had a history of wheeze and streaked sputum of 6 weeks' duration. X-ray examination showed a right-lower-lobe mass. Bronchoscopy was negative. Lobectomy (right lower lobe) was done, with the pathological diagnosis of squamous-cell carcinoma. Lymph nodes around the lower-lobe bronchus, removed with the specimen, were negative for metastases.

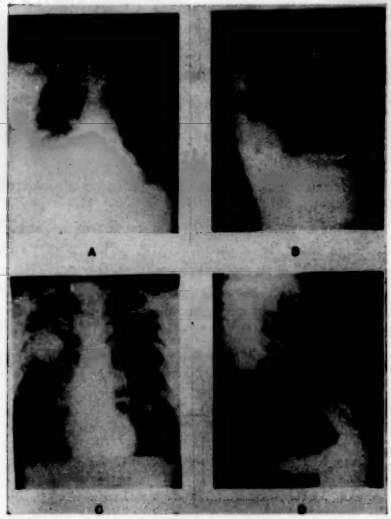

Figure 1. *Roentgenograms of the Chest in Case 1* (A *and* B) *and Case 2* (C *and* D).

Case 2 (Fig. 1 *C* and *D*). A 55-year old Negro had a history of weight loss and pain in the right side of the chest for 3 months. X-ray study at another hospital showed a small (2 by 2 cm.) mass in the right upper lobe. Two months later, on admission, the mass was larger. Bronchoscopy and extrapulmonary search for a primary tumor elsewhere were negative. The right upper lobe was excised. Pathological examination revealed metastatic hypernephroma.

Case 3 (Fig. 2 *A*, *B* and *C*). A 60-year-old man had active bilateral apical pulmonary tuberculosis. A mass was seen in the posterior basal segment of the right lower lobe in 1944. He left the hospital against advice, and was next seen 1 year later. The mass was slightly larger; the tuberculosis was quiescent, with negative sputum. Bronchoscopy was negative, and operation was advised, but the patient again left the hospital. He was admitted for the 3rd time in 1946, because of back pain. Bronchoscopy was again negative, and the mass was much larger. The tuberculosis was inactive. Pneumonectomy on the right was done, and the immediate postoperative course was uncomplicated, but the patient died of cerebral metastases in the 4th week.

These cases illustrate the importance of operation despite the absence of a positive pathological diagnosis. The patient in Case 1 has a good prognosis, and is well and working two years after operation. Another (Case 2) died eight months postoperatively, of unknown cause. The problem of other metastases in metastatic carcinoma of the lungs is ever present, but should not deter one from removing a solitary pulmonary tumor. One case of hypernephroma was seen with first evidence of metastasis, as a pulmonary tumor, thirteen years after the nephrectomy for the primary tumor. Case 3 presents the problem of tumor in addition to tuberculosis, which is seen occasionally. The important point seems to be that the tumor is usually rapidly fatal, whereas the tuberculosis is not. If the diagnosis of carcinoma can be made with a fair degree of certainty and operation is possible,

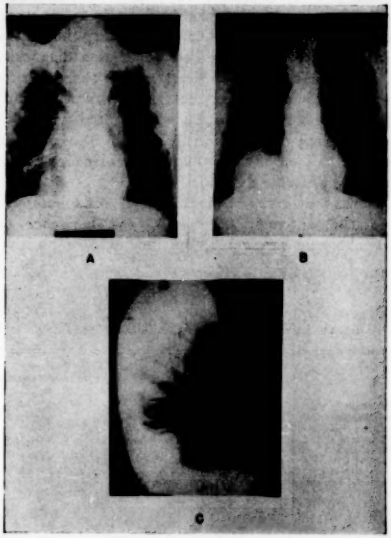

Figure 2. *Roentgenograms of the Chest in Case 3.*

the tumor should be removed, despite the tuberculosis.

Peripheral lesions resulting from bronchial obstruction, described variously as atelectasis, organizing pneumonia and fibrosis, are difficult to diagnose accurately when the bronchoscopic report is negative. In 45 such cases undiagnosed preoperatively, Johnson et al.[3] found 50 per cent to be malignant. In a similar series of 35 cases Grow, Bradford and Mahon[5] found 31 per cent malignant.

Here, too, operation is indicated in all cases, since the benign lesions are best treated by resection, in view of the irreversible parenchymal changes, such as bronchiectasis, suppuration and fibrosis.

Case 4 (Fig. 3 *A* and *B*). A 65-year-old Chinese had had cough, moderate amount of mucopurulent sputum and weight loss for 6 months. The sputum was repeatedly negative for tubercle bacilli. X-ray study showed an area of density in the left upper lobe. Bronchoscopy was negative. With a preoperative diagnosis of bronchogenic carcinoma exploratory thoracotomy was done. A parenchymal mass, palpated in the anterolateral segment of the left upper lobe, was assumed to be malignant, and a pneumonectomy on the left was done. The pathological report was organizing pneumonia. The postoperative course was complicated by pneumonitis in the right upper lobe, which responded well to chemotherapy, and the patient was discharged asymptomatic.

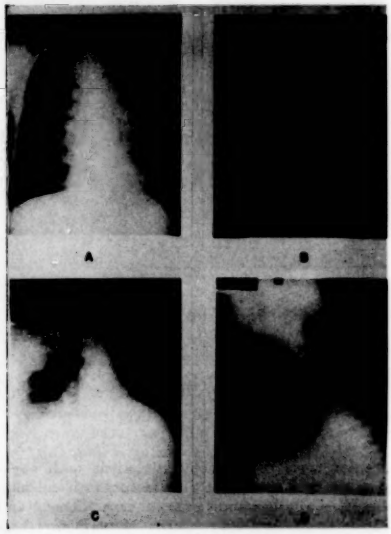

Figure 3. *Roentgenograms of the Chest in Case 4* (A *and* B) *and Case 5* (C *and* D).

Case 5 (Fig. 3 *C* and *D*). A 48-year-old man had a history of weight loss, chronic cough and small amounts of mucopurulent sputum of 3 months' duration. Sputum and gastric cultures were negative for tubercle bacilli. Bronchoscopy was negative. With a presumptive diagnosis of bronchogenic carcinoma in the apical segment of the right upper lobe, pneumonectomy on the right was done. Pathological examination revealed tuberculosis. The postoperative course was uncomplicated, and partial thoracoplasty on the right was done to diminish the volume of the right pleural cavity.

Cases 4 and 5 illustrate the problem of peripheral parenchymal masses. Even at operation, it is difficult to determine with certainty the nature of the pathologic process.[12] Therefore, it seems more rational to limit the resection to the pathologic area and to conserve as much normal lung tissue as possible. Lobectomy in peripheral tumors not involving adjacent lobes should be as curative as pneumonectomy. If the carinal and tracheal lymph nodes are involved, cure is not possible in the vast majority of cases, even with pneumonectomy. The carcinoma cells are then present in the peribronchial and peritracheal lymphatics, which cannot be removed, since block dissection, as in carcinoma of the breast, is not possible.

Cavitation may be the presenting finding in some patients. In the presence of a negative bronchoscopy, tuberculosis, lung abscess and carcinoma should be considered. In tuberculosis with cavitation the sputum should be positive, and if no acid-fast bacilli are found on repeated examination, one should be suspicious of carcinoma.

In the differentiation of lung abscess from carcinoma as the cause of cavitation, several factors may be helpful. The history in abscess is usually that of an acute respiratory illness, often following closely the administration of a general anesthetic, or an episode of loss of consciousness, such as submersion, epileptic convulsions or alcoholic stupor. The onset is usually rapid, and the illness acute, with fever, toxicity and copious sputum. In carcinoma the onset is more apt to be gradual, and although the cough may be severe, it is usually not as productive after the excavation occurs, nor is the illness as severe. On x-ray examination the abscess cavity wall usually is smooth, whereas the carcinomatous cavity usually has a rough — sometimes scalloped or serrated — inner surface. In abscess, complete subsidence can usually be obtained with antibiotics, although a residual cavity may persist, requiring further treatment. In the cavity due to carcinoma, either from bronchial obstruction or erosion of the tumor, there will be little change in its appearance after treatment.

Case 6 (Fig. 4 *A*, *B* and C). A 48-year-old man had a 15-month history of productive cough, streaked sputum, a 15-lb. weight loss and fatigue. There was a wheeze at the right apex. The sputum was negative for tubercle bacilli on repeated examination, and bronchoscopy was negative. X-ray films demonstrated progressive enlargement of a cavity in the right upper lobe. Lobectomy was done, with the finding of extension of tumor into the apical parietal pleura. The pathological report was bronchogenic carcinoma.

Case 7 (Fig. 5 *C* and *D*). A 61-year-old man had a 2-month history of cough, hemoptysis, weight loss and wheeze. X-ray examination showed a large cavity in the left side of the chest, with a fluid level. Bronchoscopy revealed pus in the left-lower-lobe bronchus, with no evidence of tumor. With a presumptive diagnosis of lung abscess, pneumonectomy for drainage was planned, but at operation an empyema was found and drained. Four weeks later, after a sudden, transient increase in sputum volume, a cavity appeared in the left lower lobe on x-ray study. Repeat bronchoscopy was

noncontributory, but carcinoma was suspected, and pneumonectomy on the left was done. The pathological report was undifferentiated carcinoma.

CASE 8 (Fig. 5 *A* and *B*). A 55-year-old man was admitted to the hospital with a 2-month history of increasing cough, mucopurulent sputum and weight loss. X-ray examination showed a cavity in the right upper lobe with a thickened, scalloped inner wall. On the assumption that the patient had pulmonary tuberculosis, he was transferred to a tuberculosis sanatorium, where the sputum was negative for tubercle bacilli and bronchoscopy revealed no abnormalities. Exploratory thoracotomy was done, with the findings of an inoperable tumor.

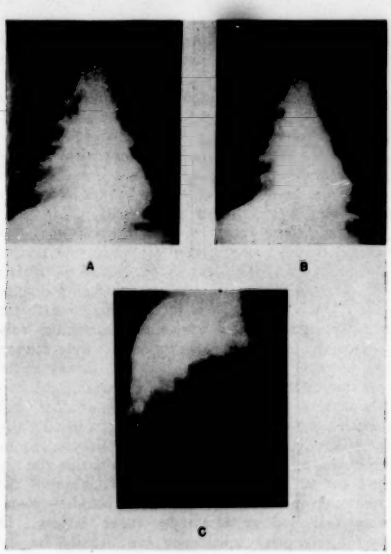

FIGURE 4. *Roentgenograms of the Chest in Case 6.*

These cases illustrate some of the problems in diagnosis when cavity is present in cases of carcinoma. None were cured, because they were explored too late. Cases 6 and 7 presented themselves for treatment too long after the onset of symptoms, and Case 8 was not explored when first seen. If, then, acid-fast bacilli are not found after adequate search, or if the suspected benign lung abscess has not shown improvement on x-ray study after treatment, exploration and resection are indicated. The chronic lung abscess is probably best treated by resection, and it seems better to resect an occasional tuberculosis lesion than to permit carcinomas to become inoperable because one is afraid that they might be tuberculous.

DISCUSSION

After repeated attempts to obtain a definite, positive diagnosis fail, surgical exploration is advisable

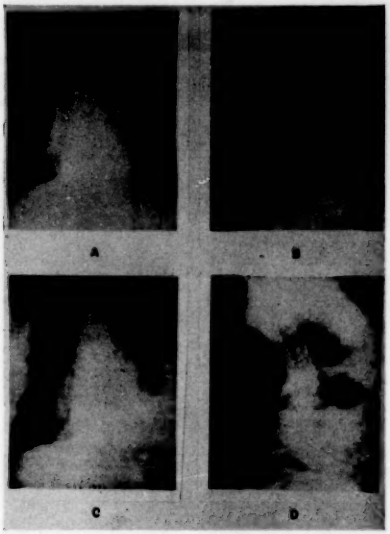

FIGURE 5. *Roentgenograms of the Chest in Case 7* (C *and* D) *and Case 8* (A *and* B).

in these cases of parenchymal lesions with negative bronchoscopy. The time factor, as in all neoplasms, is vitally important. Johnson, Clagett and Good[3] found that 28 per cent of peripheral carcinomas presenting as mass lesions and 46 per cent of carcinomas presenting as cases of bronchial obstruction were inoperable.

A survey of reported series of carcinomas of the lung reveals a low percentage of resections possible (Table 3).[1, 4, 8, 13-17] Of the total number of cases of carcinoma seen, 20 to 60 per cent of patients did not have obvious clinical signs of inoperability and were therefore explored, but only approximately 21.5 per cent were early enough to be resected. It is obvious, then, that if these rates are to be improved, earlier operation must be performed. Observation for more than four weeks in a suspected case is dangerous. In the series of 548 cases reported by Ochsner and Debakey[14] there was a positive diagnosis in 68 per cent at the time of ex-

ploration; 32 per cent of the cases were undiagnosed when operation was done. In the series of Johnson, Clagett and Good,[3] in which 384 patients were explored, there was no diagnosis in 30 per cent at the time of operation. Thus, operation must be done frequently without a positive diagnosis, which often can be obtained only by pathological examination of the resected specimen.

TABLE 3. *Operability and Resectability in Carcinoma of the Lung.*

AUTHOR	NO. OF CASES	PERCENTAGE EXPLORED	PERCENTAGE OF TOTAL CASES RESECTED	PERCENTAGE OF EXPLORED CASES RESECTED
Lindskog[4]	100	32	12.0	38.0
Graham[12]	221	51	13.0	35.0
Ochsner and Debakey[14]	548	56	36.0	63.5*
Adams[15] (Lahey Clinic)	182	—	31.0	—
Brewer et al.[5]	300	—	17.0	
Overholt and Schmidt[16]	604	60	34.0	56.0†
Lambert[17] (Bellevue)	349	20	7.2‡	36.0

*Of 195 resections, 29 per cent were considered curative, and 71 per cent palliative, at the time of operation.

†Of 162 resections, 106, or 66 per cent, had extrapulmonary extension — that is, were palliative.

‡Average, 21.5 per cent.

In a review of their series of carcinoma cases, Neuhof and Aufses[18] came to the conclusion that the peripheral tumors were less likely to have lymph-node metastases and, if there was no invasion in the chest wall, had a better prognosis. Our experience, as well as that of Clerf and Herbut[7] and Lambert,[17] agrees with this, for the cases in which bronchoscopy was negative were much less likely to have invaded the mediastinum. In general, these cases had a higher percentage of resectability. Thus, a negative bronchoscopy in a case of carcinoma of the lung may have favorable prognostic significance.

With modern methods of anesthesia, blood replacement and surgical technic, major intrathoracic surgical procedures have minimal risk. Brewer, Jones and Dolley[4] reported 1 death in 30 patients with nonmalignant cases operated on who were suspected of having carcinoma, a mortality of 3 per cent. In 200 cases, Grow et al.[5] reported no mortality in the explored cases and a 4 per cent mortality in the resected cases. In a personal series of 86 cases of all types, there was a total mortality of 4.7 per cent. In the patients subjected to exploration only, there were 2 deaths in 24 cases, or a mortality of 8.3 per cent. In the resected group of 62 cases, there were also 2 deaths, a mortality of 3.2 per cent.

CONCLUSIONS

Less than 50 per cent of carcinomas of the lung have a positive bronchoscopic biopsy, and a high percentage of peripheral lesions are malignant. The prognosis is better in most cases with a negative bronchoscopy. In the suspected case of carcinoma of the lung, early exploration is indicated especially when reversible inflammatory disease, such as tuberculosis or lung abscess, cannot be proved. Excision is indicated whenever possible, with as much conservation of normal lung tissue as possible, since most of the benign lesions are treated best by resection. All patients in whom carcinoma of the lung is a strong possibility should have the benefit of exploratory thoracotomy, since the only hope of cure is complete excision, before the tumor has spread beyond the lung.

I am indebted to Frank B. Berry, M.D., director of the Chest Surgical Service, Bellevue Hospital, for permission to use material from that service. The case reports were taken from the Bellevue Hospital series.

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TODAY'S TRENDS IN MEDICAL EDUCATION*

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BOSTON

YOUR kind invitation to talk this evening about today's trends in medical education was one I was happy to accept — not because I have any pet convictions to fan, but rather because I hoped an attempt to organize my own thoughts on the subject might be profitable. When one spends most of his time in the administrative details of a medical school, the opportunity to come up for air should be seized with gratitude, and I can think of no place in which I would rather come up for air than here in Worcester.

Worcester has always been a medically alert community. In 1796 the secretary of the Massachusetts Medical Society, which was then only fifteen years old, received a letter from one of your predecessors named Oliver Fiske; he wrote "I beg leave to inform you that a Medical Institution has been formed in the County of Worcester under the auspices of some of the principal Physicians." In 1804 the "Medical Institution" became the Worcester District Medical Society; it is said to have held regular meetings ever since and is, I believe, the oldest district medical society in Massachusetts. Exactly a hundred years ago, it extended to the Massachusetts Medical Society a "cordial invitation from the Worcester fellows, through William Workman," to meet in 1851, in what Workman described as "our small city," and it thus happened that the Massachusetts Medical Society held its first meeting away from Boston, on May 28, 1851, in the Worcester City Hall. These items, which appear in Burrage's *History of the Massachusetts Medical Society*, seemed pertinent to recall tonight in view of the fact that the Society, among other purposes, came into existence "to promote medical and surgical knowledge . . . as well as to make a just discrimination between such as are duly educated . . . and those who may ignorantly and wickedly administer medicine."

Although this concern for the processes of medical education was recorded by the Massachusetts Medical Society in the latter part of the eighteenth century, the nineteenth came and went before real progress was initiated. This nation grew quantitatively, too fast and too free to become sensitized to the quality of its medical care. We need only go back to 1900 to find medical education in a chaotic state. To be sure, there were good (not good by today's standards, but honestly operated) schools, perhaps 50 of them, but there was no screen by which these 50 could be separated from the 160 or more that were doing business in the United States at the turn of the century; the infamous diploma mills were then in full swing.

We all know the story of the Flexner report and the reform that swept away those proprietary schools. A few cobwebs were left in the corners, but on the whole the medical schools that survived the first quarter of the century did so because they were able to pull themselves up, generally under the aegis of a university, but in a few notable instances by their own bootstraps. Some figures that fall into the first quarter of the century indicate the magnitude of the changes that then took place. The number of medical schools in active operation was cut in half (from 162 in 1906 to 79 in 1924). In eighteen years the annual numbers of graduates decreased 56 per cent (from a high of 5747 in 1904 to a low point of 2529 in 1922). The number of medical graduates holding S.B. or A.B. degrees rose from 15.3 per cent in 1910 (the first year for which figures are available) to 61.2 per cent in 1925. This increase in the percentage of doctors holding first degrees in arts or sciences emphasizes the speed with which the study of medicine assumed the status of postgraduate education; by 1930 the percentage of medical graduates who also held a bachelor's degree had risen to 70; it has since crept higher.

So by the 1930's medicine had established itself in the United States as a graduate study. This meant that it had built itself, for better or for worse, into the pattern of university education. In the four years of college thus prescribed, however, there are less than two years of technical premedical study — the rest is supposed to be cultural. The medical schools, if not the colleges, have tended to defend this extra two years of cultural exposure as being necessary to ensure sufficient background and maturity in the medical student body. The requirement is not a hard and fast one, and exceptions to it are not infrequently made in the cases of certain students. The validity of the background and maturity achieved in the junior and senior years of college study is not uniform and is difficult to appraise. No fixed program of premedical study has yet completely vindicated itself. In the 1920's one medical school undertook to operate its own premedical program; it failed, but that does not mean that the idea is bad or that it might not be made to succeed in the 1950's. May there not be a *medical* culture that none of our colleges or universities has yet tried to establish, the sort of culture that appears in page after page of the

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eighth edition of Osler's *Principles and Practice*, that might crystallize itself only in a system under which the history of medicine, with its many ramifications, became a required and fundamental discipline instead of an elective diversion? The best that we can say about today's trend in premedical study is that it is sufficiently elastic to permit each student to take advantage of his opportunities for a liberal education. The worst that can be said is that it holds many students in college two years longer than they need to be held to attain the minimum technical preparation for the study of medicine.

When we come to the selection of medical students from among the thousands who apply for admission we reach a subject upon which there is a good deal of divided opinion, especially within the profession. For example, a few weeks ago a doctor whom we all recognize as having a good deal of insight told us that we "exclude the good ones" in order to take what we take. From time to time this may well be so, and one can sympathize with the implication of this criticism. The medical schools, however, are making investments in these students. If in the end they cannot pass their state and national board examinations all the personality and fine character that would make them good doctors is lost to the profession. Such a loss is great, not only for the student who has been unfortunately selected but also to the schools and to society. It may sometimes be true that the schools look too critically at the scholastic grades that candidates have achieved, but it is also true that those who do the selecting are fully as interested in the personal characteristics of their candidates. The selective process is not cut and dried, is not scientific and cannot be made to operate on any precise criteria, but of one thing we may be sure: the selection, good or bad, predetermines the quality of the output to a greater degree than anything else in the vast system of medical education to which the candidate selected is subsequently exposed.

The educational standards that have been established during the past forty years have had a very great influence upon the output of the medical schools. There was first a sharp reduction in the number of doctors produced, accompanied by an increase in the quality of the graduates. This was followed by steady increases in both quantity and quality of output. The question of doctor shortages has been agitated a good deal lately. There is today no question that we need more doctors, not because our health is threatened, for it was never better or more secure, but because there are a great many more things that doctors may be called upon to do. Doctors used to confine themselves to seeing sick people, and in the 1920's trained themselves with that in mind; today many of them see only well people. Industries, governmental services, hospitals, insurance companies, great funds and foundations striving to help mankind, colleges, universities and others in increasing numbers are hiring doctors who are primarily concerning themselves with well people. Some of these are in a way being paid to stay away from the sick. Doctors are thus becoming more and more constructive members of the community from an economic and social point of view, and it seems plain that the investments that medical schools are making in their training are completely justified. The standards are not too high, but there is one very serious drawback — the medical schools are going bankrupt in the process.

This is the crisis of the moment in medical education. The financial position of the medical schools is rapidly deteriorating. At least 48 of America's 78 schools operated in red ink in 1948, the total deficit approaching $10,000,000. Thirty-eight of these 48 schools are privately operated by colleges or universities.

How can this be so? The reasons have been explored rather thoroughly; they boil down to the following:

An increased tax burden has undermined support formerly given by individual philanthropy.

A falling yield for endowment capital has brought about a decline in such income.

A sharp rise in cost of operation and maintenance has taken place during and since the war.

Considerable expansion of plant and technical equipment has been necessary since the entry of medicine into the scientific areas of chemistry, physics, pharmacology and so forth.

What is being done about it? Since the war there has been much discussion of the subject. There seem to be three general sources from which some increased revenue might be expected.

The first source, and the one to which any businessman would turn, would be the annual tuition fee. One cannot ordinarily stay in business selling something for less than it costs, but if we charged the medical student what it costs we would make medical education too precious; we would exclude all but the few who could pay such high fees. It is probable that the tuition fraction of the cost has already been expanded as far as it can be. This is certainly true if a wide choice of recruits are to be attracted to the profession. In the School with which I am most familiar the tuition was raised from $300 to $350 in 1928, to $400 in 1930, to $500 in 1936, to $600 in 1947, to $675 in 1948 and to $800 in 1949. We very much hope that there will be no further increase, but this must depend upon whether other sources of support can be amplified or new ones found.

The second source that is being talked about is the one to which everybody seems to turn these

days — that is, Government subsidy. Last year bills were drawn to provide for federal support of medical education in the amount of $500 per student per year for a period of five years. The details of these bills were the subject of a good deal of discussion, and they were passed by the Senate just before the first session of the Eighty-First Congress adjourned. By the time Congress reconvened, however, opposition had developed in the American Medical Association, owing to the fact that there were more differences to be adjusted before a solid medical front could be obtained. This accounts for delay in the passage of the legislation, but if satisfactory safeguards and limitations can be set up we may expect some federal aid for medical education in the near future. It seems to have bipartisan support at the present time, and it is admittedly emergency legislation if it is passed.

The third source of possible support is one that has been quietly organized by a relatively small group of distinguished citizens, but as yet no announcements concerning it have been made and publicity has been avoided. A voluntary agency known as the National Fund for Medical Education has been incorporated. Its board of trustees includes outstanding examples of the nation's powerful business, labor and professional leaders. The National Fund embraces an imaginative concept of corporate citizenship and philanthropy; it conceives of a system in which the great industrial and mercantile corporations of America would voluntarily support medical education as a national enterprise. Such support might permit the free survival of a function that was formerly dependent upon private philanthropy, but is now in danger of having to choose between modest governmental subsidy or extinction. If medical and allied science can turn toward this sort of corporate philanthropy, the possible disaster of governmental control might be converted into a triumph of democracy and a continuation of educational freedom in medicine. Obviously this is more easily said than done, but the founders of the National Fund seem to be convinced that they can contrive a way of doing it, and within the next few years we may see this great effort consummated in a substantial investment of America's brains and resources in medical education.

If one could be reasonably happy about the methods of selecting students and about the financing of their education, the millennium would not have arrived, for there still would be perennial discussion concerning the content of the curriculum. Jacob Bigelow used to tell Harvard Medical School graduates at the end of their two years' instruction that they need have no fear of the adequacy of their preparation. He assured them that they knew all there was to know about medicine and surgery. This was probably so in 1870, and if they had taken to heart Bigelow's lecture "On Self Limited Diseases" they would have been, in some respects, fifty years ahead of their time. As knowledge gathered, the orthodox medical course was extended to three years, to four years and in some schools to a required fifth year of internship. By 1920 practically everyone took the fifth year, required or not, and most of them took more. Now, of course, knowledge has expanded far beyond the capacity of one person, and yet the course remains of four years' duration. It is therefore obvious that instead of the whole we are imparting a smaller and smaller fraction of available medical knowledge. Instead of the family-style table, at which everybody sits down to the same food, the medical schools must now pick and choose *à la carte* from a rather complex menu. We can no longer reassure our graduates as Jacob Bigelow did; indeed, in all conscience we must impress upon them that they do not yet begin to know what they must learn if they are going to compete in the modern practice of medicine and surgery.

Modern practice calls for an interest in the specialized fields, if not participation in them, and medical-school teaching should embrace this interest even though it cannot hope to encompass the technicalities involved. Many consider the medical schools as a central point of origin from which each specialized group within the profession must spring. This can be so only in the sense that the primary grades are the point of origin for all educated people. When we turn for help and advice to those who know most about the specialized fields, we sometimes find that we have to watch our basic philosophy or we lose it. For example, the Association of American Medical Colleges was told by a committee of specialists a few years ago that their special subject should have devoted to it 5 per cent of the teaching time, but 8 per cent of the teaching budget. In some circumstances this might constitute a wise allocation of available resources, but as a blanket recommendation it suggests professional bias.

The groups that constitute what we now regard as the various specialties are of two sorts. They are either the standard, exclusive type of specialty that limits itself with anatomic and physiologic boundaries, or they are interests so broad and inclusive as to spread themselves the length and breadth of the curriculum. For these latter the orthodox departments and courses are both inadequate and unnecessary; the indication for such interests is to infiltrate and establish themselves as a sort of fifth column in the already established major divisions of medical teaching. Industrial medicine is an example. In practice some industries need a toxicologic type of service, others need an expert and immediately available organization for traumatic surgery including facilities for subsequent rehabilitation, and still others will need primarily the sort of health and placement services that can be best supplied by the internist or the

general practitioner. The interests of such a specialty may be well served by postgraduate courses, associations, societies, academies, colleges, institutes and conventions, but this does not mean that in order to vouchsafe its integrity there must also be an undergraduate medical-school department and course in the subject. If industrial medicine is to be referred to as a specialty it should be accepted as an inclusive one, and one that is distinguishing itself from other forms of practice through its economic philosophy rather than its professional activity.

For twenty-five years there has been recurring effort to emphasize the social aspects of medicine. Most of this effort has been ineffectual because rapidly growing scientific demands and accomplishments have overshadowed it, but it has nevertheless produced some of our enduring medical literature. Peabody's *Care of the Patient* and Worcester's *Care of the Aged, The Dying and the Dead* are examples; a quarter century of progress has not dulled their pages (which is more than can be said for most medical literature). How these social aspects of medicine can be worked into the four-year span has been the subject of some recent study by a committee of the Association of American Medical Colleges. This study has shown that there is a widespread desire to emphasize the importance of the social and economic background of illness. It is probable that this aspect of medicine cannot be effectively taught in the absence of what are referred to in theology as the "graces of the spirit." These graces are largely inborn, but we believe them to be as abundant in medical schools as in schools of religion. The difference is that in medical schools both teacher and student tend to be preoccupied with what seem to be urgent technical matters. Whether these are actually as urgent as they seem is beside the point; they do absorb most of the medical student's energy and time, because they constitute the framework of the examinations to which he must submit himself if he hopes to qualify before the various state boards of medical examiners.

One member of our faculty is an ardent believer in student participation as a way of life in medical school. He extends this belief to the execution of a complete immunizing program among the students, and utilizes the data thus obtained to teach the potential value of such programs. He likewise promotes student blood donations to the Red Cross, having arranged for the collection of more than a hundred pints at each of the annual donor clinics held at the School in recent years. There is in all of this a social, as well as a pedagogic value. Participating citizens are good citizens, and so are participating doctors.

Summary

These are some of the things that seem to have sufficiently established themselves to be indicative in medical education:

A continuing gradual increase in both the quality and quantity of the graduates of our schools.

A selective process that will seek to recruit the most fortunate possible combination of scholastic aptitude and personal qualification among those who are chosen to enter the schools.

A rapidly fulminating crisis in the financial pattern of medical education, the reasons for which have been stated.

An earnest effort to meet this crisis without further increase in tuition fees, either by public (federal) or private (corporate) support.

An effort to integrate the subject matter of the curriculum in such a way that special technics are subordinated to basic philosophies and scientific backgrounds.

There is a distinct tendency to emphasize the social aspects of medical practice, and to place before the student body the validity of personal participation in community affairs.

Trends are sometimes tenuous and difficult to identify. Here I have tried to select some of the things toward which we may look realistically and hopefully. I hope they have sufficed for a not too long evening. Medical education is grateful for your interest; we hope it will continue in the future, as in the past.

TREATMENT OF CONGESTIVE HEART FAILURE IN AMBULATORY PATIENTS WITH SALYRGAN-THEOPHYLLINE ADMINISTERED ORALLY*

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IN ANY outpatient cardiac clinic are to be found considerable numbers of patients who must report to the hospital for injections of mercurial diuretics as often as several times each week. The present study was motivated by a desire to relieve many of these people of this burden.

The patients in this study were entirely unselected except that they all gave evidence of severe congestive failure requiring mercurial diuretics for maintenance. Most had been receiving mercurial injections once or twice a week. Others had needed one only every four to six weeks. At the other end of the scale was a patient who required 2 cc. intramuscularly every other day. All were treated on an ambulatory basis, and all received standard therapy in the form of digitalis, ammonium chloride and low-salt diet without fluid restriction. No other diuretic drugs besides ammonium chloride and mercurials were administered. The oral mercurial used was Salyrgan-theophylline in tablet form.¶ For convenience it is referred to below as STO (Salyrgan-theophylline Oral).

TABLE 1. *Cardiac Diagnoses.*

DIAGNOSIS	NO. OF PATIENTS
Rheumatic heart disease	7
Hypertensive heart disease	2
Arteriosclerotic heart disease	2
Hypertensive arteriosclerotic heart disease	15
Syphilitic heart disease	2
Cor pulmonale	1
Arteriosclerotic heart disease, with unexplained murmur of perhaps congenital or rheumatic origin	1
Total	30

The efficacy of treatment was evaluated by the usual subjective criteria of dyspnea, cough and paroxysmal nocturnal dyspnea, but more especially by objective criteria such as body weight, edema, pulmonary rales, hyperpnea, palpable liver and ascites. A constant watch was kept for such toxic symptoms as have been reported[1-3] — namely, gingivitis, nausea, vomiting, diarrhea and abdominal cramps. Regular urinalyses and blood counts were performed, in addition to occasional stool examinations for occult blood.

Thirty patients were studied, 10 females and 20 males, whose ages ranged from thirty-nine to seventy-eight years and averaged sixty years. They were followed for an average of twelve months, ranging from three to thirty-seven months. Table 1 presents the distribution of cardiac diagnoses in the group.

After stabilization of patients on STO, control tests were performed. These tests consisted of the omission of mercurial diuretics for one to three weeks or the substitution of a placebo for like periods. In some patients both tests were performed at different times. The need for mercurial diuretics was adequately proved by the prompt appearance of dyspnea or weight gain and edema, or all three, during the control periods.

In changing from parenteral to oral mercurials for maintenance the proper dose of STO for some patients could be rapidly determined. Other patients required a longer trial period before complete transition from parenteral to oral administration could be effected. In the cases in which by chance the correct or approximately correct oral dose was prescribed immediately, the transition from injections could be made abruptly, with little discomfort to the patient. Otherwise, supplementary injections were continued for varying periods. For the first year of study, the supplementary injections were continued in more patients and for longer periods than was true later. The attempt was made later to replace the injections completely whenever possible.

As found by others,[4] complete individualization of dosage is necessary with oral administration of mercurial diuretics. Moreover, the oral dose of the preparation is not proportional to the patient's previously required maintenance dose and frequency of parenteral administration.

Most of the patients were started on a schedule of 1 tablet three times a day after meals for three successive days each week. If no diuresis resulted, 3 tablets in one dose were administered after breakfast for three successive days. It was found on several occasions that when given three times a day STO did not result in diuresis but that 3 tablets in an undivided dose did. This is as yet unexplained. When a patient reported diuresis from a given dose, and objective evidence indicated a need for more, the number of successive days of administration

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¶Kindly supplied by Winthrop-Stearns, Incorporated, New York City. Each tablet contains 0.06 gm. of Salyrgan (representing 0.0317 gm. of inorganic mercury) and 0.04 gm. of theophylline.

was increased rather than the number of tablets taken each day. It was considered advisable to give oral administration of the mercurial diuretic intermittently in order to give the patient a rest period of one to four days each week, and thus to allow excretion of any mercury that may possibly have accumulated. Batterman et al.[5] employed a rest period of a week between monthly courses.

It was observed that it was necessary to administer the effective diuretic dose for each week on successive days. The oral administration of the drug on alternate days was unsuccessful. It was also unsatisfactory to change, for example, from four successive days each week to two-day periods separated by a free interval of two or three days. Rarely tried were other schedules, such as 2 or 3 tablets three times a day or 2 tablets in an undivided dose every day.

The largest undivided dose administered was 8 tablets. The largest daily dose employed consisted of 5 tablets three times a day, given six days each week. This dose of 90 tablets a week was taken by 1 patient for a week, omitted for a week and then taken for four successive weeks without ill effects. This is the largest dose noted by us in the literature.

These large doses were prompted by the impression that sufficient dosage would produce diuresis even in apparently refractory cases. It appeared safe to proceed in view not only of previous work[1] on patients with congestive heart failure but also of extensive toxicity experiments on animals.[6]

Table 2 lists the dosage schedules that were ultimately arrived at for most of the patients in the group.

STO completely replaced parenteral injections successfully in 17, or 57 per cent, of the 30 patients. Some of these 17 have now been followed for periods up to three years. In 9 more cases STO was at least partly successful. It is believed, on the basis of subsequent experience, that complete replacement could probably have been accomplished by a slight increase in the relatively small doses that 2 of these patients took. In 2 others, injections were required only during acute infections or other unusual stress. In a patient who had required a 2-cc. injection every other day, complete substitution with oral tablets could be accomplished for periods up to four weeks at a time. In the other 4 cases, owing to very low cardiac reserve, regular injections of mercurial diuretics were required, though at less frequent intervals than previously.

The remaining 4 cases represent failure of STO. Two of these occurred in patients with severe rheumatic heart disease whose cardiac reserve was too low for them to be comfortably maintained with mercurial diuretics in any form. In such situations the tablets cannot be expected to help either, as observed by Batterman et al.[5] The other 2 failures of STO were due to the development of distressing gastrointestinal symptoms.

In 4 notable cases STO was successfully employed to dehydrate the patients to "dry weight," with the loss of as much as 24 pounds of edema fluid. After this initial dehydration the dose was carefully decreased for maintenance by cutting down the number of days each week on which STO was taken.

Confirming the observations of others,[2, 7] the concurrent use of ammonium chloride usually improved the diuresis obtained with oral administration of mercurial diuretics. However, ammonium chloride was definitely incriminated as the cause of gastric irritation in 4 patients, 2 of whom voluntarily omitted the medication. The other two take only 1 0.5-gm. tablet of ammonium chloride three times a day. All 4 continue to have adequate diuresis with STO.

TABLE 2. *Dosage Schedule of STO.*

No. of Tablets	Times per Day	Period of Dosage *days/wk.*
1	3	3*
1	3	4
1	4	5
2	3	4
3	1†	4–6
4	1†	3–4
5	1†	4–5
6	1†	2–4
Up to 8	1†	5–6
4	2	4–6
5	2	4–5
5	3	6

*Three successive days each week.
†Undivided dosage.

Many patients definitely subscribed to the opinion that oral administration, besides improving their general status, helped their morale. It is believed that this sense of well-being was due to a more constant level of compensation with STO than the more fluctuating levels attained with intermittent injections.

Three patients are now free of the severe muscle cramps previously experienced after parenteral administration, even in 1-cc. doses. One of these had also experienced chills after mercurial diuretics had been administered intravenously in another clinic.

Another interesting sidelight is the case of the seventy-one-year-old woman who obtains adequate diuresis with STO. She now has a daily bowel movement, without diarrhea or other distress, after years of constipation. This is a common experience with STO.

No toxic effects were observed in the blood counts or urinalyses. Albuminuria, a very frequent finding in such patients with congestive failure, showed no increase under treatment, although the usual fluctuations noted in congestive failure were ob-

served. Gingivitis developed in 3 patients, clearing in 1 when STO was stopped for two weeks and more attention was given to oral hygiene. It never recurred in this case after resumption of STO. Another patient's gingivitis cleared with better oral hygiene and without omission of STO. The third patient was lost to the clinic, and no further information is available. It is our opinion that proper oral hygiene is adequate to prevent or to treat the gingivitis observed with STO therapy.

Table 3 indicates the relative incidence of gastrointestinal symptoms, which were relatively minor in 10 of the 15 patients. The cases not considered

TABLE 3. *Toxic Gastrointestinal Symptoms in 15 Patients.*

SYMPTOM	NO. OF PATIENTS
Nausea	5
Vomiting	4
Diarrhea	7
Crampy abdominal pain	6
Tenesmus	1
Bleeding	
Tarry stools	2
Gross blood in stools	1
Rectal burning	1

minor were the 3 with bleeding and the 2 previously mentioned as treatment failures. One of these 2 patients experienced excessive gastric irritation, and the other excessive diarrhea. The latter represents the only case in which it was necessary to discontinue STO therapy because of toxic effects. In all patients except the last 2, symptoms usually cleared quickly, often without temporary omission of STO. Occasionally, the symptoms recurred for a brief period, only to disappear again just as quickly. The transient nature of these toxic symptoms has been reported by others.[1, 2, 5]

Two patients noted tarry stools for one to three days after four and a half and six and a half months, respectively, under STO therapy. One patient did not report the symptom until two weeks after its occurrence. It had already cleared during the two weeks, during which he had continued to take STO. The other patient with tarry stools, after a week without STO, resumed therapy without recurrence for three months.

The occurrence of gastrointestinal symptoms was a matter of individual difference and was not always related to the size of the dose of STO. In addition, a single daily dose might produce discomfort whereas the same amount divided into three or four doses might not.

One patient reported bright-red blood in the stools after three months on oral mercurial therapy. Treatment was stopped for two weeks, during which sigmoidoscopy revealed "hemorrhagic proctitis" manifested by many tiny punctate hemorrhagic spots on the mucosa. Barium enema and repeat sigmoidoscopy were reported as normal. There has been no recurrence for six months.

Sigmoidoscopy was performed, in addition to the occasions already noted, on 6 patients who were taking the larger amounts of STO. All were reported as normal. The dosages ranged from 25 to 60 tablets a week at the time of sigmoidoscopy. In still another patient, complete x-ray series of the upper gastrointestinal tract and barium enema revealed only "colonic spasm," with normal mucosal pattern.

There were 4 deaths in the group. One man of sixty-four who had severe angina pectoris died suddenly while walking in the street after several months of successful STO therapy. Another, a thirty-nine-year-old woman who had had rheumatic heart disease for eighteen years, died in congestive failure one and a half months after the omission of STO. She had not been helped by a three-month trial of STO or by frequent injections of mercurial diuretics. The third was a man of sixty-two with hypertensive arteriosclerotic heart disease and a history of two myocardial infarcts. After fifteen months of STO therapy he was admitted to the hospital with a tentative x-ray diagnosis of bronchogenic carcinoma. He died very suddenly in a manner believed by the attending house staff to have been characteristic of pulmonary embolism.

The fourth death occurred in a man of fifty-seven with arteriosclerotic heart disease. After eighteen months' use of STO he was admitted to the hospital because of sudden, severe hematemesis. Exsanguination brought on his death in four days despite treatment. At post-mortem examination, the significant findings were an ulcer of the cardioesophageal junction and multiple superficial ulcers of the entire colon. The kidneys showed no mercurial damage. There was definite cirrhosis, but esophageal varices could not be demonstrated. It was believed that the cardioesophageal ulcer might have been part of the so-called Mallory–Weiss syndrome (a lesion secondary to vomiting). As for the ulcerations in the colon and rectum, the pathologist[3] considered it unlikely that mercury could be incriminated in the absence of microscopical evidence of mercurial nephrosis.

SUMMARY AND CONCLUSIONS

Thirty ambulatory patients with congestive heart failure were treated with STO (Salyrgan-theophylline Oral) for an average of twelve months, the duration of therapy ranging from three to thirty-seven months.

STO can successfully decrease the patient's burden in reporting to the clinic either by decreasing the need for frequent mercurial injections or by actually replacing the injections entirely.

The use of STO improved the general status and also the morale of most of the patients in the group.

The dosage must be completely individualized. STO can effectively dehydrate to dry weight.

Failure with oral administration occurred in 4 cases, possibly owing to excessively decreased cardiac reserve (when parenteral administration of mercurial diuretics was of little help), to insufficient dosage or to toxic symptoms that precluded further use of the medication.

Very large doses may be well tolerated. The largest amount used in this series consisted of 5 tablets three times a day for six successive days (90 tablets) each week for a month.

Toxicity is manifested by gingivitis and by varied gastrointestinal symptoms but does not necessarily prevent further effective and harmless use of the mercurial diuretic orally. Only 1 patient in the group could not tolerate repeated trials of STO because of excessive diarrhea.

There were 4 deaths. Three were directly traceable to the cardiac conditions. Some of the postmortem findings in 1 of these were consistent with what has been described as occurring with mercurialism. However, the absence of typical nephrosis makes the responsibility of mercury somewhat debatable.

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BILE PERITONITIS COMPLICATING NEEDLE BIOPSY OF LIVER*

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ASPIRATION or punch needle biopsy of the liver is a recognized diagnostic procedure. In research in recent years, in an attempt to correlate liver function and histopathology, this method of obtaining biopsy material has become increasingly popular.

That the procedure is not without some danger has been recognized by almost all groups, but the complications have been few enough so as not to dishearten the majority. The observation of Kinsell et al.[1] that the blind approach to a highly vascular, bile-secreting, intraperitoneal organ can never be devoid of risk is indeed candid. Some groups, such as Mateer and his associates,[2] have been reluctant to subject their patients to even 1 chance in 200 or 300 of a serious accident from this diagnostic procedure, and have used the aspiration needle only at time of laparotomy.

There have been 17 deaths as a result of needle biopsy in over 4900 cases reviewed (Table 1). This constitutes a mortality of 0.35 per cent, being slightly less than Sherlock's[10] 0.67 per cent and Hoffbauer's[20] 0.49 per cent.

Roholm, Krarup and Iversen[8] first comprehensively listed and considered the possible complications of aspiration biopsy. They included pain,

Table 1. *Mortality in Aspiration Biopsy of the Liver.*

Author	No. of Biopsies	No. of Deaths	Complications
Bingel (1923)[3]	100	2	Hemorrhage (2 cases)
Olivet (1926)[4]	140	3	Hemorrhage (2 cases)
Toullec and Huard (1935)[5]	Not stated	1	Hemorrhage due to peritonitis (1 case)
Baron (1939)[6]	48	1	Hemorrhage
Koffer (1940)[7]	100	2	Hemorrhage (2 cases)
Roholm et al. (1942)[8]	297	2	Hemorrhage (2 cases)
Dible et al. (1943)[9]	(126)		
Sherlock (1945)[10]	264	2	Hemorrhage (2 cases)
Raby (1944)[11]	Not stated	2	Hemorrhage (2 cases)
Gillman and Gillman (1945)[12]	507	1	Hemorrhage
Volwiler and Jones (1947)[13]	278	1	Hemorrhage
Totals	1734	17	
Additional series reporting no mortality[14-19]	3177		
Total number of biopsies	4911		

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damage to neighboring organs, implantation of tumor cells in the needle tract, air embolus, infection, bile peritonitis and hemorrhage. Of the 17 fatal cases reviewed, 16 were due to hemorrhage and 1 to peritonitis, apparently secondary to intestinal perforation.

Greene[34] and Hoffbauer[32] have mentioned the leakage of bile into the peritoneal cavity as a potential danger, especially in the presence of obstruction of the biliary tract, although this has never been observed by them. Sherlock,[10] Hoffbauer,[32] Kumpe et al.[33] and Volwiler and Jones[13] have suggested the use of aspiration biopsy as a means of differentiating obscure types of jaundice. Cogswell and his co-workers,[26] in a recent consideration of the contraindications of needle biopsy, did not mention jaundice.

Case Report*

A 51-year-old married man was admitted to the hospital with a chief complaint of jaundice and anorexia. He had been well until 5 months before entry, when he had had bronchitis with fever, which lasted for 2 weeks. At this time jaundice was first noted. He returned to work despite the jaundice and continued to work until 5 days before admission. During the 5-month period there had been continuous jaundice, anorexia and progressive weakness and a 15-lb. weight loss (150 to 135 lb.). The stools had been light, and the urine dark yellow. Five days before admission the patient had felt very weak, had become nauseated and vomited, but on bed rest and forced fluids he had felt somewhat improved.

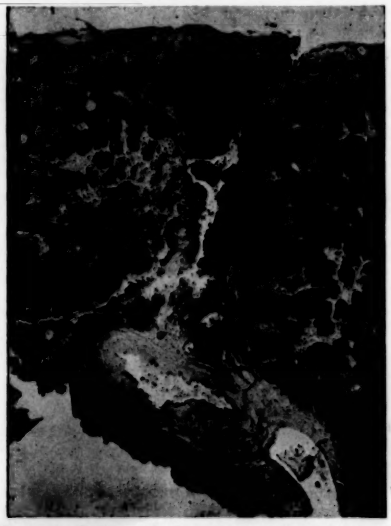

Figure 1. *Section of the Liver Surface with the Fistula Extending to the Subserous Bile Duct (x10).*

*We are indebted to Drs. H. G. Dunphy and J. R. Lyman for permission to report this case.

There was a history of excessive alcoholic intake for the past 30 years. The remaining past history was noncontributory.

Physical examination revealed a thin, well developed man with marked icterus of the skin and scleras. The lungs were clear. The abdomen was scaphoid, and the liver edge was smooth and palpable 15 cm. below the right costal margin. The liver moved with respiration and was nontender. The remainder of the physical examination was within normal limits.

The temperature was 100.6°F., the pulse 96 and regular, and the respirations 24. The blood pressure was 110/70.

Examination of the blood disclosed a red-cell count of 3,600,000, with a hemoglobin of 11.8 gm., and a white-cell count of 13,000, with a normal differential and normal platelets. The bleeding time was 7 minutes, and the clotting time 2½ minutes. The urine showed a strongly positive test for bile and was positive for urobilinogen in a 1:32 dilution. The nonprotein nitrogen was 33 mg., and the blood glucose 120 mg. per 100 cc. The total protein was 7.4 gm. per 100 cc., with 2.1 gm. of albumin and 5.3 gm. of globulin. The alkaline phosphatase was 13.2 King-Armstrong units, and the phosphorus 3.4 mg. per 100 cc. The prothrombin time was 100 per cent of normal. The serum bilirubin was 11.2 mg. per 100 cc. direct and 23.3 mg. indirect. A stool was light brown and negative for occult blood.

The patient was ambulatory and was given supportive therapy. It was decided that liver biopsy was the most direct approach to establishing the etiology of the hepatomegaly. He received intramuscular injections of vitamin K and Demerol. He was taken to the operating room, and a site just below the right costal margin over the enlarged liver was infiltrated with 1 per cent novocain. With the Franseen biopsy needle two specimens were taken, since the first was inadequate. The surgeon noted that the patient complained of a rather unusual amount of pain after the specimen was taken.

The patient was kept on strict bed rest for the next 24 hours, but complained of increasing abdominal pain and required sedation. There was a gradual increase in abdominal distention over the next 3 days. The abdomen was tympanitic, with slight spasm. The patient appeared acutely ill, and the white-cell count rose to 23,400. X-ray examination of the abdomen revealed distinct distention of some small-bowel loops, with a tendency toward ladder pattern. There was some gas in the colon. These findings were suggestive of ileus, with a possibility of peritonitis. The temperature remained between 99° and 100.° A Miller-Abbott tube was passed, and Wangensteen suction maintained. Nutrition was maintained by intravenous injection of fluids, and 125 gm. of serum albumin; penicillin and streptomycin were given without effect. The patient died seven days after the liver biopsy.

The biopsy specimen consisted of three fragments of brownish tissue 8, 6 and 5 mm. in length respectively and each 2 mm. in diameter. The microscopical diagnosis was portal cirrhosis of the liver, alcoholic type.

An autopsy was performed 2 hours post mortem. Below the costal margin to the right of the midline of the abdomen there was a needle puncture wound. The peritoneal cavity contained 8000 cc. of turbid, dark-yellow, watery fluid, in which numerous strands of dark-yellow-brown fibrin floated. This material was adherent at points to the peritoneal surfaces.

The liver weighed 1820 gm. and was of usual size and shape. Near the anterior apex of the dome of the right lobe and in relation to the needle puncture wound in the abdominal wall was a linear scratch, 1 cm. in length and 1 mm. in width, and leading from this surface injury was a minute sinus tract, which on section extended approximately 1.5 cm. into the parenchyma (Fig. 1). From this wound oozed clear, watery bile. No hemorrhage was evident. Section revealed the liver to be moderately increased in consistence and to cut with a firm, gritty sensation. The lobular architecture was slightly accentuated, the lobules standing out as yellow-brown spots against a slightly increased yellow-gray interlobular background. The intrahepatic bile ducts were dis-

tended with bile. The portal and hepatic vessels were not remarkable.

The gall bladder was distended by approximately 100 cc. of thick viscid black bile and in itself was not remarkable.

The common bile duct was 1 cm. in diameter, and the ampullary orifice was obliterated. The ampulla was the site of an ulcerated, hard neoplasm, 2 cm. in diameter, which was not fixed to the underlying pancreas or adjacent retroperitoneal structures. The common bile duct entered the tumor, and there was no demonstrable bile channel into the intestine.

Microscopical sections from the surface of the liver in the area of the needle puncture wound revealed the surface to be covered with amorphous débris containing bile-stained material. Immediately beneath the surface was a broad zone of proliferating fibrous tissue in which were occasional bile canaliculi and small bile ducts. In the area of the needle wound was a large bile duct that contained amorphous débris and whose wall appeared disrupted at points.

Sections from the ampulla showed the bile-duct epithelium to give way to an ulcerated neoplasm composed of fairly well defined, gland-like units of epithelial cells, some of which were producing mucus. These cells showed moderate variation in size, shape and staining reaction and small numbers of mitoses. The tumor was extending well into the muscularis, and there was definite local lymphatic invasion.

The complete final pathological diagnoses were as follows: adenocarcinoma, Grade II, of ampulla of Vater; obstruction of common bile duct; bile peritonitis; pancreatic necrosis of retroperitoneal fat, slight; cirrhosis of liver, mixed type, portal and biliary; bronchopneumonia, minimal, aspiration type; chronic cholecystitis, slight; atherosclerosis, slight, of aorta; and jaundice.

Discussion

The accompanying photomicrograph (Fig. 1) is of the fistula and the anterior surface of the liver. It is seen that this tract extends down to a bile duct of unusually large caliber for its proximity to the hepatic serosa. Attention is called to the artery, which is adjacent to both the bile duct and fistula.

Iversen and Roholm,[37] Baron,[6] Sherlock,[10] Hoffbauer,[32] Kumpe et al.,[35] Volwiler and Jones[13] and Sanes and his associates[38] have all repeatedly performed punch liver biopsy in the presence of obstructive jaundice without any serious complications from the extravasation of bile. Beierwaltes and Mallery[39] report accidental penetration, without untoward results, of the gall bladder through the overhanging edge of the liver in a case of carcinoma of the head of the pancreas. On one biopsy attempt Kumpe et al.[35] obtained 3 cc. of bile on aspiration, apparently from a large biliary radicle, but there were no ensuing complications.

Cope[40] has suggested the following factors that normally tend to prevent any extensive extravasation of bile through a perforation: the low pressure of biliary secretion and its intermittency, and the natural tendency to closure of any abnormal opening in the muscular body tubes, even more striking in the hepatic ducts than elsewhere in the body. However, if there is obstruction at the ampulla of Vater, there is a rise in the interductal pressure.

Bile peritonitis without perforation has frequently been reported. On the basis of experimental work Pohlmann[41] stated that a perforation of the biliary system is necessary, but may be difficult to demonstrate. McLaughlin[42] supported Pohlman's observations and demonstrated in man ruptures of subserous bile ducts in association with common-duct obstruction.

Dible et al.,[9] surveying 6 fatal cases following aspiration liver biopsy, noted that there were no deaths in the nonjaundiced cases, but believed that biopsy was justifiable in the investigation of jaundice of obscure etiology. His group and Iversen and Roholm[37] agree that fatal hemorrhage may occur in severely jaundiced patients.

The case of bile peritonitis reported above demonstrates another complication of punch liver biopsy in the presence of long-standing jaundice.

Summary

The mortality of punch needle biopsy of the liver is briefly reviewed. Seventeen deaths in over 4900 biopsies are noted, a mortality of 0.35 per cent.

Biliary fistula with bile peritonitis, a possible but heretofore unreported complication, is illustrated by a case reported in detail.

The possibility of the creation of a biliary fistula by penetration of a superficial bile duct should be considered.

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MEDICAL PROGRESS

ALLERGY

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THERAPEUTIC advances in allergy have failed to keep pace with the development of antibiotics in the field of infectious disease. Yet it must be remembered that the underlying nature of the allergic state is still imperfectly understood and that control of altered reactivity is a more complicated matter than inactivation of bacteria alone. Progress in allergy has not been dramatic, but it has made forward steps, as shown in part by rapidly expanding interest in the subject both by the medical profession and by the laity. Membership in allergy societies and attendance at medical conferences devoted to allergy have increased tremendously on sectional, national and international levels. An increasing proportion of the public is gradually becoming aware that the handling of the allergic problem is not a matter of performing a large number of skin tests leading to a miraculous cure. The patient with severe allergic disease is beginning to learn from his own experience and from that of fellow victims that he is suffering from a chronic constitutional and probably inherited disease that can be better tolerated if he will cooperate in a prolonged program of allergic management. He is discovering that — to guide such a program intelligently — his physician should have a sound training in medicine as well as in allergy and a sustained interest in his patient's recurrent symptoms. Such a patient does not have to be convinced of the need for further large-scale efforts in trying to discover ways of helping him. Progress has been slow, however, in organizing an appeal to the public for aid in carrying on much needed projects in research and clinical investigation. Asthma is not the leading cause of death, but the patient with severe asthma sometimes wishes that it were. There is hope that the tread of a march of dimes or a cry to give from the heart may yet be heard in behalf of sufferers who sneeze, wheeze and itch.

Brief comprehensive summaries of progress in allergy are no longer possible. Such a review as this must be limited to one particular field such as hay fever,[1] bronchial asthma,[2] miscellaneous allergy[3] or pediatric allergy[4] or to specific topics of current interest. This discussion concerns the broader aspects of the antihistaminic problem and a review of preliminary reports of the use of ACTH (adrenocorticotrophic hormone) in allergic disease.

ANTIHISTAMINICS

The antihistaminics were first made available to the public on physician's prescription in 1946, and by the first part of 1948, several thousand cases treated with the earliest of these drugs had been

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reported in the literature with discussion of their mode of action, comparative merits, side reactions and dangers.[5-8] In the meantime, many new antihistaminic agents have appeared, and articles concerning them have become so numerous that several comprehensive reviews have been published on this subject alone.[9-11] There is considerable discrepancy between the reports of different observers concerning comparative results obtained with the same antihistaminic agents, from the standpoint of both efficacy and the production of side reactions. Many factors, known and unknown, bring this about and help to increase the difficulty of establishing uniform standards for clinical control. Most observers seem agreed, however, upon the following general observations drawn from the mass of literature. The antihistaminic agents are particularly effective in the edema-producing types of allergy[12] such as urticaria, angioedema, serum disease, seasonal hay fever and, to a less degree, perennial vasomotor rhinitis. Their role in asthma has been very disappointing.[2] Here they have failed to hold their place with the other drugs such as epinephrine, ephedrine, aminophylline, potassium iodide and Isuprel. Antihistaminics are of value in many of the itching dermatoses, in which they help to control the pruritus and thereby diminish further trauma to the skin from scratching. The antihistaminic preparations sometimes act as anesthetics and strong sensitizers when applied locally. They often have a cholinergic and a sedative action when administered by the parenteral route. These drugs are only palliative, and their effect is temporary, lasting with most agents but three or four hours. More recent preparations sometimes afford relief for as long as twelve to twenty-four hours.[13, 14] Antihistaminic drugs may be used topically in the eyes, in the nose,[15, 16] on the skin[17] or by aerosol administration.[18] They may also be given intravenously. This is seldom a recommended procedure, for toxic reactions are more frequent and severe when this method is employed.[19-21] Oral medication is readily absorbed, is effective and is adequate in most cases.

The degree of efficacy and the likelihood of side reactions is unpredictable in any given case. It is always possible that a shift from one antihistaminic preparation to another will produce more satisfactory clinical results. Side reactions are common, appearing between approximately 10 and 60 per cent of cases when administered in adequate therapeutic doses.[20, 22] These symptoms, the commonest of which is drowsiness, may cause the patient minor inconvenience or may be severe enough to necessitate discontinuance of the drug.[19, 20] Dangerous reactions continue to be reported.[19-26] Variability in the efficacy and in the appearance of side reactions of the antihistaminics emphasizes the desirability that these agents be prescribed and used under competent medical guidance. Several years' experience with them has established their value as a supplementary aid in the treatment of certain types of allergy. It has likewise been demonstrated that the drugs do nothing to hyposensitize the patient to substances to which he may be sensitive, nor does their administration in hay fever do anything to prevent the later development of pollen asthma. Neither should the antihistaminics take the place of well established procedures of allergic management such as careful search for and, when possible, elimination of offending allergens.

Consideration of the antihistaminic drugs is particularly timely now that recent wide publicity has been accorded the new antihistaminic cold cures. These may be purchased over the counter without a physician's prescription. Newspaper and radio advertisements have boasted that such preparations are almost certain to prevent or cure the common cold as well as to be perfectly free from all dangers. These pronouncements followed the publication of a few papers reporting a high percentage of relief of symptoms after the administration of antihistaminic preparations during the early stages of a cold.[27-29] The validity of these extraordinary claims of efficiency of antihistaminic cold cures appears doubtful in view of the recent report of two series of cases controlled by careful clinical investigation.[30] Statistics have already been quoted and are readily available regarding the percentage occurrence of side reactions with various antihistaminic agents.[20] Only elementary arithmetic is therefore necessary to confirm the prediction that wide, uncontrolled use of these drugs is certain to be followed by side reactions of varying intensity in a considerable portion of the large section of the population that is doubtless hopefully purchasing them.

Evidence is rapidly accumulating that self-administration of these advertised cold cures is not invariably attended with success and that side reactions are not uncommon. Reports of the latter are already beginning to appear. The Council on Pharmacy and Chemistry of the American Medical Association,[31] in a status report on these agents, has warned against indiscriminate use of antihistaminic substances that are now being promoted for the prevention of colds and even for treatment of those suffering from colds. This type of advertising direct to the public is a menace to public health in that its exaggerated claims fail to warn of the potential dangers of medication, particularly overmedication, a safeguard that is usually provided by the physician. Unexpected side reactions experienced by seekers of a cold cure may bring out a "never again" response should this type of drug later be prescribed for treatment.

ACTH Therapy

Progress in research and clinical investigation in the so-called collagen diseases has been startling. The discovery by Hench and his co-workers[32, 33]

that the administration of certain substances of the adrenal cortex (compound E or Cortisone) and adrenocorticotrophic hormone (ACTH) of the pituitary gland was followed by dramatic improvement in rheumatoid arthritis and rheumatic fever touched off universal medical speculation about the possible benefits that might be anticipated with the use of these products in allergic disease. Only a few cases with asthma and other allergic manifestations similarly treated have as yet been reported in the literature, but others are in publication and investigators throughout the country are carrying out carefully controlled clinical studies in this group of diseases as rapidly as the preparations become available. These preliminary reports published since early 1949 are briefly reviewed.

Bordley and his associates[34] noted that Hench et al.[33] had given ACTH in a case of acute rheumatic fever with subsidence of fever within forty-eight hours and disappearance of articular symptoms within four days. Rich and Gregory's earlier experimental work had already, on the basis of pathological studies, suggested a relation between the rheumatic diseases and the hypersensitive state. These combined observations pointed to further exploration of the possible usefulness of ACTH in allergic disease. Administration of this hormone to a patient with severe exfoliative dermatitis due to iodine and to one with a serum-disease type of penicillin sensitivity was followed by rapid recovery. Stimulated by these results Bordley et al. treated 5 cases of chronic asthma with ACTH in doses of 30 to 100 mg. daily, maintained for eleven to twenty-one days. Complete freedom from all asthmatic symptoms occurred within one to eight days. Nasal polyps disappeared under treatment in 1 case and nearly disappeared in another, only to recur in the former twenty-three days after the cessation of therapy. Positive skin tests were diminished in 1 case but returned to their original level three weeks after ACTH had been discontinued. In a later communication, the same authors[35] noted recurrence of asthmatic symptoms in all these patients, with subsequent relief after a second course of ACTH.

Rose et al.[36] gave ACTH to 6 patients with intractable asthma, each of whom had been observed for at least three years. Four of these patients obtained complete relief from all symptoms, the longest of which was for a month. In the other 2 only partial relief was achieved. The signs and symptoms of rheumatoid arthritis in 1 case and of periarteritis nodosa in another were markedly improved. From the same clinic[37] comes a report of a case of Loeffler's syndrome and one of tropical eosinophilia in both of which the circulatory eosinophils showed a decided drop after ACTH therapy. There was marked clinical improvement in the former case but none in the latter until the patient received an arsenic preparation. Rose[38] discussed the results of ACTH therapy in 10 patients with allergic manifestations including asthma, urticaria, allergic rhinitis, periarteritis nodosa and acute disseminated lupus erythematosus. Unsatisfactory clinical improvement was noted in 4, and in no case did remission of symptoms last over six weeks, no matter how long treatment was continued.

Thorn and his co-workers[39] cite marked temporary clinical improvement in 3 patients with acute disseminated lupus erythematosus treated with ACTH, as well as in 9 patients with rheumatoid arthritis and 1 with gout. They review the major metabolic changes induced in man by the administration of ACTH in the presence of an intact adrenal gland and point out the wide variation in the state of adrenocortical function that appears to exist from patient to patient irrespective of the severity or manifestations of the disease. The danger of long-continued, high-level treatment is emphasized, but it is suggested that with 40 mg. of ACTH daily this danger is minimal although adequate adrenocortical activation is achieved.

Elkinton et al.,[40] reporting on ACTH therapy, included a five-year-old boy with status asthmaticus who showed marked improvement. Of 2 patients with disseminated lupus erythematosus, 1 maintained a fairly complete remission for sixty days after the end of administration of the drug; the other became refractory to ACTH and died. The authors call attention to the development of other complications such as Cushing's syndrome, potassium deficiency and encephalopathy and warn that the therapeutic use of ACTH must be approached with great caution. Sprague and his associates[41] present a fifty-nine-page report of 33 cases, largely of rheumatoid arthritis and acute rheumatic fever, treated with Cortisone, ACTH and, in 1 case, Compound F. This paper has direct interest for those concerned in allergy, since the authors discuss in detail the profound physiologic effects of Cortisone and ACTH and point out that decision about their use in therapy will require a careful balance between what is indicated from the standpoint of the disease in question and what is best for the over-all welfare of the patient.

There is thus already ample evidence that administration of ACTH can produce dramatic temporary cessation of symptoms in allergic disease comparable to that already shown with ACTH and Cortisone in rheumatoid arthritis and rheumatic fever. Wide publicity of early reports to this effect should not lead to the hasty conclusion that the problem of allergy is about to be solved, for investigators have indicated[42] that the fundamental process by which ACTH and Cortisone affect these diseases is unknown and unmeasured in the terms of the known metabolic functions of the adrenal cortex and that, whereas they may produce dramatic remissions in these diseases, their use may also be attended by serious complica-

tions. A dramatic stimulus has been given to clinical research in allergy. The role of these substances in further investigation in allergic disease will be watched with great interest.

Summary

Progress in allergy, with particular reference to a broadening interest in this branch of internal medicine, is reported.

The present status of the antihistaminic drugs is briefly reviewed. A warning is issued about unexpected side reactions likely to occur from antihistaminic cold cures widely advertised and sold directly to the public.

Early preliminary reports on ACTH therapy in allergic disease are summarized and discussed.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 36281

PRESENTATION OF CASE

First admission. A fifty-one-year-old woman was admitted to the hospital complaining of hematuria of 2 days' duration. This was associated with the passage of numerous small clots, and, shortly after its rather sudden onset, the hematuria became complicated by a dull, constant, incapacitating pain in the left upper quadrant of the abdomen radiating to the left midaxillary line in the region of the twelfth rib. In spite of a weight loss of 6 pounds in the preceding six months, her general health had been excellent. Physical examination revealed a well developed, well nourished woman. The chest was clear, and the heart not enlarged. A Grade I aortic systolic murmur was transmitted to the neck. A firm, lobulated, nontender mass, which moved with respirations, was palpable in the left flank. This extended downward from the costal margin to the umbilical line and laterally from the midclavicular line to the midaxillary line. An intravenous pyelogram disclosed a large mass obscuring the lower pole of the left kidney, and on the sixth hospital day a left nephrectomy was performed; the kidney contained a renal-cell carcinoma, 9 cm. in diameter, which replaced the lower pole, was densely adherent to the renal capsule and invaded the renal pelvis. No involvement of the renal vessels or ureter was found.

Final admission (five and a half years later). The patient was in excellent health until five days before admission, when she experienced the rather sudden onset of chills and vague abdominal pain unassociated with gastrointestinal or urinary symptoms. The abdominal distress persisted, and on the day before entry she again had an attack of chills. Fever was denied during this period. On the morning of admission she awoke with severe generalized abdominal pain and vomited twice. Later that morning the temperature was 102.2°F. Her physician found that the abdomen was diffusely tender with moderate spasm in the left flank. A questionable irregular mass extended 4 fingerbreadths below the left costal margin. The abdomen was tympanitic throughout, but peristalsis was active and of normal pitch. An enema produced considerable relief of pain. Later in the afternoon the temperature was 99.8°F., and a rectal examination was negative. At 10:00 p.m., however, there was a sudden recurrence of severe generalized abdominal pain. The abdomen was tense and diffusely tender. Peristalsis was absent. Micturition at this time produced dark, concentrated urine. Because of these symptoms the patient was readmitted to the hospital.

Physical examination disclosed an obese, confused woman with considerable abdominal pain. Examination of the heart and lungs was negative. The abdomen was distended, tympanitic and tender throughout. There was muscle spasm in the left flank and a suggestion of a grapefruit-sized mass in this region. Slight bilateral costovertebral-angle tenderness was present.

The temperature was 102°F., the pulse 90, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

The urine had a specific gravity of 1.028 and gave a +++ test for albumin, and the sediment contained an occasional erythrocyte and 3 leukocytes per high-power field. Examination of the blood revealed a hemoglobin of 12.0 gm., and a white-cell count of 8600, with 85 per cent neutrophils. The nonprotein nitrogen was 38 mg., and the serum protein 5.0 gm. per 100 cc., the chloride 92 milliequiv. per liter, and the prothrombin time 70 per cent of normal.

The patient continued to run a febrile course. On the second hospital day she became more distended and began to vomit coffee-grounds material. The abdomen was diffusely tender, with spasm and almost completely absent peristalsis. A Miller–Abbott tube inserted at this time could not be passed beyond the pylorus. A plain film of the abdomen showed considerable gaseous distention of the small bowel. When the examination was repeated on the following day both the small and the large bowel were distended with gas, and there was a suggestion of increased intra-abdominal fluid. There also appeared to be a mass in the left flank. The white-cell count had risen to 11,300, with 88 per cent neutrophils. Because of continued distention a cecostomy was performed on the fourth hospital day but the patient remained markedly distended. That evening she became confused, disoriented and more acutely ill. The pulse rate rose to 120, and the respiratory rate to 30. There were signs suggestive of atelectasis at both lung bases, and the abdomen was distended, tympanitic and silent. On the fifth day the

hemoglobin had fallen to 10.0 gm., and a 500-cc. transfusion of whole blood was administered. Since she had failed to respond to the large doses of penicillin and streptomycin given since admission, antibiotic therapy was changed to aureomycin. This likewise failed to alter the clinical course. A paracentesis in the right flank on the sixth day yielded 5 cc. of amber, turbid fluid from which abundant *Pseudomonas aeruginosa* (*B. pyocyaneus*) and moderate *Staphylococcus aureus* were cultured. At the same time an attempt to aspirate the mass in the left flank yielded soft, brown matter, and it was thought that the colon had been entered. Although the patient remained extremely ill and no peristalsis was audible, she began to pass loose bowel movements, and the abdomen became slightly less distended. The hemoglobin was now 11.4 gm., the hematocrit 30, the white-cell count 34,300, the chloride 93 milliequiv. per liter, and the serum protein 4.6 gm. per 100 cc. Fifty grams of serum albumin was administered. On the tenth hospital day the patient became semistuporous. On the eleventh day, dyspnea became more marked, and cyanosis of the nail beds and lips developed. On the twelfth day there were numerous moist rales throughout the left chest, and on the following day a chest x-ray film showed fluid in the right pleural cavity, reduction in size of the right middle and lower lobes and prominence of the hilar regions. The vascular markings throughout the left lung were increased, and the heart was transverse in position. The chloride at this time was 88 milliequiv. per liter, and the protein 5.0 gm. per 100 cc. A thoracentesis performed in the seventh interspace, right midaxillary line, yielded bloody fluid thought to be from the liver. Aspiration at a higher plane yielded first flecks of thick, gray material followed by 250 cc. of serosanguineous fluid. The blood pressure fell, the pulse became more rapid and irregular, and death occurred on the thirteenth hospital day. Throughout the illness the patient had remained febrile, with fluctuations between 101 and 104°F. The urinary output was considered adequate at all times.

Differential Diagnosis

Dr. William C. Quinby, Jr.*: This woman had an acute, progressive, fatal abdominal disease, which failed entirely to respond to our present armamentarium of antibiotics, decompression therapy and intravenous support. I think in such cases a very careful study must be made of the history and early physical signs, because the physician who comes in late on such a case is so confused that he cannot possibly make a diagnosis.

In the past this patient had had a renal-cell carcinoma, but she had excellent intervening health and notably no constipation, no cholecystic attacks or anything that could be interpreted as such, and no symptoms indicative of peptic ulcer. She was described as being obese on the final admission.

The illness started with a chill, but no fever was noted. The very slight abdominal discomfort and chill were repeated, and only four days later she was seen with the severe generalized abdominal pain and fever that, although relieved by an enema, recurred within twelve hours. On examination early in the course there was distention of the abdomen, generalized abdominal tenderness and a mass in the left flank, and it was only there that there was some spasm suggesting a localized lesion. Peristalsis was heard on the morning of the day of onset of severe symptoms, was absent in the afternoon and really never returned thereafter. The routine laboratory studies, with a low white-cell count, a slight shift in the Schilling differential to the left and a urine compatible with almost any abdominal crisis give us no localizing lead. The chemical laboratory studies do not help either — just a low protein.

This was an acute illness, without any real localizing symptoms from the past history, and manifested by fever, severe adynamic ileus, and a questionable mass in the left flank. I think the next step on the ward and now had better be to see this questionable mass in the x-ray films.

Dr. Stanley M. Wyman: The films show the tube in the stomach and a moderate quantity of gas in both large and small bowel. The small bowel is very slightly distended. There is no evidence of frank obstruction at that time. There is an indefinite soft-tissue density overlying the left flank, but a clearly defined mass cannot be outlined. Calcified mesenteric lymph nodes are present. On the second examination distention of the small bowel has increased, and there does seem to be some suggestion of the ground-glass density associated with fluid. The film of the chest shows a rather large quantity of fluid in the right pleural space, compression and atelectasis of the right lower lobe and probably some degree of vascular engorgement of the lungs.

Dr. Quinby: Was either of these films taken in the upright position?

Dr. Wyman: No; they were both taken horizontally.

Dr. Quinby: I still fail to see the mass.

Dr. Wyman: It cannot be outlined well, but I think it lies in this location.

Dr. Quinby: Thank you, Dr. Wyman.

In the x-ray films there is again the suspicion of a mass, fluid and bowel dilatation. As time went on the efforts to decompress this patient with the Miller–Abbott tube and even by cecostomy were unavailing. An abdominal tap was done following the cecostomy and on the same side. I think the bacterial flora found — *B. pyocyaneus* and staphylococcus — are more characteristic of the skin than they are of a severe intra-abdominal sepsis.

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We are not told what the dark-brown material found in the mass on the left side was. Was it feces? I suppose that I shall have to possess my soul in patience on that score, but when something is obtained from the abdomen, it should always be smeared.

The differential diagnosis of acute, progressive, fatal, abdominal illness revolves about the following categories: perforation of a hollow viscus, obstruction, perforation of an abscess, infarction of some organ or pancreatitis. In this case, I think I can eliminate gastric, small-bowel, gall-bladder or even ovarian-cyst perforation. There was no evidence of misplaced air, and no preceding ailment indicative of disease of those organs. However, the large bowel, particularly in the region of the splenic flexure, might have been the source of a perforation.

I do not believe the patient had obstruction of either large or small bowel, at least as a primary entity. The vomiting had been very late in the game. The film taken on the second hospital day is really not the film of an acute localized small-bowel obstruction. There is no gas in the colon; there is no dilatation of the colon proximal to the descending colon, at any rate. The ileus was of an adynamic type and was not obstructive.

An abscess in the abdomen could perforate a little at first and produce a chill and then could rupture and cause a generalized peritonitis. But there was no primary source for abscess unless it was a recurrence of the renal-cell carcinoma. It customarily is a tumor that recurs rather late. There have been many recurrences after five or six years, but to tie it into a picture of adynamic ileus I would have to postulate some marked insult to the tumor. Then, too, the patient had been in excellent health. I am going to dismiss it, probably with regret.

Among the other diseases that will cause an acute surgical abdomen are infarction of a solid organ and infarction of the bowel. Mesenteric thrombosis is a peculiar disease and can give a picture exactly like this, frequently being confused with intestinal obstruction in which an early stage of premonitory symptoms, followed by a sudden severe episode, occurs. This story was a little too long for mesenteric thrombosis. The patient lived too long, but perhaps our modern therapy prolonged her life. The temperature was too high at first for that disease. Characteristically, the white-cell count is higher. However, I think it is entirely possible that she had a mesenteric thrombosis.

Pancreatitis is a second severe abdominal disease that is always confusing. This would necessarily have had to be the subacute form or the acute form involving only part of the pancreas at first and then spreading to the rest of it. In this event I think there would have been jaundice present and symptoms appearing sooner. Our staff showed marked restraint in doing as few blood chemical determinations as they did if they suspected a pancreatitis. I am sure I would have had more than one amylase determination to help me with that diagnosis. Pancreatitis characteristically is a disease with symptoms referred to the epigastrium. The flank is rather low. I think I cannot really put much weight on acute pancreatitis in this case.

There is one other thing that I should like to mention. Patients can have a perforated diverticulum of the colon, without previous bowel symptoms, that causes an initial chill and goes on to local abscess formation and large-bowel obstruction. I think in this case the lack of pus in the abdomen on cecostomy, the lack of any previous clinical history of bowel disturbance and the failure to respond to decompression efforts and heavy antibiotic therapy would steer me away from that diagnosis.

I do not know what this patient died of. I think my first choice is mesenteric thrombosis on the venous side. I think that mesenteric thrombosis in at least a quarter of the cases shows masses almost anywhere in the abdomen. What are these masses? Frequently, they are necrotic bowel. I cannot exclude a tie-up with a previous renal carcinoma, but I shall do so and make my final diagnosis acute venous mesenteric thrombosis. Notably, this disease has very few causes except possibly previous abdominal surgery, customarily done on the same hospital admission on which the mesenteric thrombosis occurs.

Dr. Alfred Kranes: Would mesenteric thrombosis be likely to start with chill?

Dr. Quinby: The intra-abdominal illnesses that start with chill and produce this picture are very few, but, as I said, mesenteric thrombosis can start with a chill.

Dr. F. Dennette Adams: Is mesenteric thrombosis more likely to have cramps at the beginning like obstructive lesions?

Dr. Quinby: Yes; particularly when very small areas are involved at first. Some people will have an episode marked by cramps lasting perhaps two weeks and from which they recover.

Clinical Diagnosis

Diffuse peritonitis.
? Recurrent hypernephroma.
? Diverticulitis.

Dr. Quinby's Diagnosis

Mesenteric thrombosis, venous.

Anatomical Diagnosis

Recurrent hypernephroma invading wall of descending colon, with multiple intraperitoneal abscesses from perforation of bowel in this region by toothpick.

Pathological Discussion

Dr. Tracy B. Mallory: At the time of autopsy it seemed very remarkable that the cecostomy

could have been done without disclosing pus in the abdomen because we found about 20 intraperitoneal abscesses of all varying sizes, each isolated between adherent loops of bowel. It was quite evident that there had been a generalized peritonitis at one period that had just begun to localize, with the formation of multiple abscesses. The largest one was in the pelvis, the next largest was beneath the diaphragm, and a third one was just lateral to the descending colon. In this area we found recurrent tumor, the bulk of which was lying in the bed of the nephrectomy site but a portion of which had invaded the wall of the descending colon, producing several polypoid masses within the lumen. These were not large enough to have caused as yet any severe degree of obstruction. However, they may well have been responsible for the arrest in this portion of the bowel of a foreign body, approximately half of a broken toothpick. This had eroded the bowel wall and penetrated the tumor, producing a false diverticulum, with abscess formation. This abscess in time had ruptured into the peritoneal cavity, with the production of general peritonitis, which subsequently localized to produce multiple peritoneal abscesses.

CASE 36282

Presentation of Case

A thirty-eight-year-old housewife was admitted to the hospital because of increasing fatigue and an enlarged spleen.

The patient was well until three and a half years before entry, when her second child was born. The labor was somewhat difficult, and soon after the delivery she began to have swelling of the ankles, with red, swollen, tender toes. She had not felt entirely well since that time and had had soreness of the wrists, elbows and toes intermittently. During the three and a half months prior to entry she had noticed increasing fatigability, which had become of such degree that she had to give up housework. A physician found an enlarged spleen.

The patient had had the usual childhood diseases but denied rheumatic fever or chorea. She had had psoriasis since the age of fourteen. There was no history of palpitations, dyspnea or orthopnea. There had been no weight loss.

Physical examination disclosed a well developed and well nourished woman who appeared younger than her stated age. The heart showed a sinus tachycardia, a loud mitral first sound, a Grade II apical systolic murmur and a Grade I apical presystolic rumble. There was a split mitral second sound, and the aortic second sound equaled the pulmonic. The lungs were clear. The liver was just palpable under the costal margin and was smooth and nontender. The spleen was palpated four fingerbreadths below the costal margin and was smooth and hard. The second right toe was red, swollen and tender with crepitus. There was crepitus in several other toes also.

The temperature was 98.5°F., the pulse 120, and the respirations 20. The blood pressure was normal.

The urine had a specific gravity of 1.012 and was otherwise normal. Bence-Jones protein was absent. The blood hemoglobin was 11.4 gm., and the white-cell count 7400, with 52 per cent neutrophils, 1 per cent large lymphocytes, 40 per cent small lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. There was moderate variation in the size of the red blood cells. A blood smear showed 0.4 per cent reticulocytes. The red cells were generally normocytic and slightly hypochromic, with slight anisocytosis and poikilocytosis. There was no basophilia. The white cells appeared somewhat reduced in number and were qualitatively normal except for 4 per cent atypical cells, which were somewhat between mononuclear cells and normal large lymphocytes. The platelets were significantly reduced in number, and giant forms were present. No nucleated red cells or immature white cells were seen. Bone-marrow aspiration of a spinous process revealed 1 or 2 per cent reticulocytes. There were 56 per cent myeloid cells, 35 per cent erythroid cells and 9 per cent lymphocytes with a myeloid-erythroid ratio of 1.6:1. Myelopoiesis and erythropoiesis were orderly, and no fat-storage cells were seen. Megakaryocytes were abundant and platelets were scanty. The sedimentation rate was 24 mm. in 1 hour. A fragility test showed no hemolysis in 0.50 per cent sodium chloride. The bleeding time was 1 minute. The clotting time was reported as 5 minutes in the first tube, 9 minutes in the second and 12 minutes each in the third, fourth and fifth tubes. The clot retraction was normal. The serum nonprotein nitrogen was 21 mg. per 100 cc., the total protein 6.37 gm., the albumin 4.32 gm., the globulin 2.05 gm. (albumin-globulin ratio of 2.1), the alkaline phosphatase 3.8 units per 100 cc. and the cholesterol 219 mg. per 100 cc., and the prothrombin time 19 seconds (normal, 17 seconds). A Congo-red determination showed 85 per cent retention in the serum, the cephalin-flocculation test was ++ in twenty-four and forty-eight hours, and the bromsulfalein test was 12 per cent. The blood Hinton test was negative.

Roentgenograms of the hands, shoulders and knees were negative. X-ray films of the feet showed a generalized demineralization and narrowing of the proximal interphalangeal joints. There were destructive changes about the interphalangeal joints of the first toes on both sides, as well as about the distal interphalangeal joint of the right second toe and the proximal interphalangeal joints of the third, fourth and fifth toes. These changes consisted of a subchondral necrosis with narrowing of the joint space. There was also lipping at the joint margins and a hallux-valgus deformity bilaterally. A gastrointestinal series showed a normal esophagus,

and no varices were demonstrated in the lower third on two separate examinations. The stomach was displaced anteriorly and toward the midline by a markedly enlarged spleen, which extended to the iliac crest. There was slight enlargement of the liver. An electrocardiogram showed slightly prominent P waves.

In the hospital the patient remained symptomatically unchanged. On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. John R. Graham*: Perhaps you would show the x-ray films, Dr. Wyman.

Dr. Stanley M. Wyman: The films of the feet are slightly overpenetrated to demonstrate the bony changes very well, but there are definite areas of subchondral bone destruction. The joint spaces appear unusually wide, however. The bones are somewhat osteoporotic. The hands, knees and shoulder joints show no definite intrinsic disease. The heart is generally slightly enlarged and shows particular enlargement of the left auricle, which is seen in the lateral view extending posteriorly. The hilar vascular shadows are more prominent than usual. The picture is quite consistent with rheumatic heart disease. The spleen is enormously enlarged, extending down to the iliac crest and displacing the barium-filled stomach medially and slightly anteriorly. The esophagus is very well seen in these spot films and shows no evidence of varices.

Dr. Graham: Would you characterize these joint changes as anything special?

Dr. Wyman: They look like multiple areas of bone destruction in the subchondral areas adjacent to the joint spaces. There is generalized soft-tissue thickening about the abnormal areas in the bones.

Dr. Graham: There is no doubt about the subchondral destruction?

Dr. Wyman: There is no doubt in my mind whatsoever. I do not think it is specifically pathognomonic, however.

Dr. Graham: This case is a little unusual in that I find that I cannot decide what the operation was that was performed. Usually in these cases one has a good idea of what the physicians on the ward were interested in doing to increase their knowledge, but I am inclined to suppose that their interest lay chiefly in finding out the cause of the enlarged spleen. Since there are several approaches to that problem, I cannot predict what the operation was, but I would guess that probably, in view of the history, a laparotomy was done in which both liver and spleen could be biopsied and the lymph nodes in the abdomen could be examined. However, liver biopsy or splenic puncture or peritoneoscopy might be alternatives.

There are several points in the history that I would like to emphasize. One is that the patient seemed to have the symptoms and findings of both rheumatic heart disease and rheumatoid arthritis. I think the murmur and the x-ray findings are so characteristic of mitral stenosis that we must say that this patient had rheumatic fever and rheumatic heart disease. The joint changes, which I believe had been present three and a half years, certainly seem more like rheumatoid arthritis than anything else, and the joint changes noted on x-ray study in the regions where the patient had most of the symptoms seem to fit in with that. I am inclined to think that, whatever else this patient had, she was one of the small group of patients who have both rheumatic fever and rheumatoid arthritis.

The next point is the increase in symptoms for the three and a half months previous to entry, to the point that the patient had to stop work — a rather marked increase in fatigability. The next is the spleen, enlarged to the brim of the pelvis, that seemed to be the center of attraction. Along with this was a slightly enlarged liver with some evidence of impaired liver function in the bromsulfalein test without abnormalities in any of the other liver-function tests. The fourth point is that the blood and bone-marrow findings were relatively normal, with perhaps a suggestion of some inhibition of delivery of the white cells and platelets to the peripheral blood, which is not infrequently seen in people who have enlarged spleens for various reasons.

I start on this problem wondering whether this person had one or two or three diseases depending on whether one calls rheumatic heart disease and rheumatoid arthritis one or two diseases. Did she have that combination in addition to something else, or was it all part and parcel of the same picture? Let us consider for a moment the possibility that the patient had two separate conditions with something new and different responsible for the

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spleen and liver enlargement. The laboratory data, the lack of any significant anemia and the reticulocyte count rule out congenital hemolytic jaundice quite well. The patient did not present the appearance of thrombocytopenic purpura. The symptoms in that disease are usually those of purpura, and the spleen tends to be small rather than large — at least not very much enlarged. One might consider cirrhosis, in which it seems to me it would be rather unusual to find so large a spleen. Also, there was not much disturbance in the protein and albumin-globulin ratio, and even the cephalin-flocculation test was within normal limits so that I am inclined to think that cirrhosis was not the trouble.

Obviously, the clinicians wondered about Banti's disease. The patient was carefully checked for varices, which were not found, so that I am inclined to think that Banti's disease is unlikely.

Then I might mention a group of diseases in which enlarged spleens are known to occur such as infectious mononucleosis, malaria and histoplasmosis. Tuberculosis, of course, can involve the spleen, and sometimes is found to cause quite large spleens even when the tuberculosis in the rest of the body is minimal. Syphilis is known to involve both liver and spleen and can cause a very large spleen but in almost all those cases the blood Hinton test is positive. Doan's hypersplenism usually presents itself as a leukopenia. I do not think the leukopenia in this case was marked enough, and the spleen is not usually so large as this was. One wonders a little bit about the so-called agnogenic myeloid metaplasia. Cases of that sort that I have seen have begun either as polycythemia, with an enlarged spleen, or with a picture in the peripheral blood suggesting a leukemia. The bone marrow, which was examined, did not suggest the changes seen in that condition. Gaucher's, the Niemann–Pick and Hand–Schüller–Christian diseases are characterized by a generalized disturbance of the reticuloendothelial system, and I would expect to find the characteristic large cells either with or without storage of fat in the bone marrow.

One has to pause more thoughtfully over the possibility of whether this was some form of leukemia engrafted on a person who had rheumatic heart disease and rheumatoid arthritis. In this category my attention is attracted by the possibility of a monocytic leukemia. We have seen several cases of monocytic leukemia in which the peripheral blood failed to show abnormal cells for some months. I can remember one* presented in this conference that showed only an enlarged liver and some enlargement of the spleen. In that case the liver biopsy was the determining factor in the diagnosis. This idea has some attractive points because something had happened to this woman in the last three and a half months that made her a good deal sicker than she had been. Yet I am inclined to believe that if she had been so sick with monocytic leukemia that she had had to stop all her housework she probably would have been at a point where some abnormal cells would be found in the blood and in the bone marrow.

Lymphoma, of course, might present these findings, might cause the increased fatigability and might present this course and still not affect the peripheral blood or bone marrow so that I consider that with a good deal of seriousness.

I am inclined to put this together in one box if possible. I see no real reason why this could not be Felty's syndrome, which is known to occur with the combination of rheumatic heart disease, rheumatoid arthritis and an enlarged spleen with peripheral leukopenia. It is a little unusual to find quite so large a spleen with Felty's syndrome; however, a case was described in which the spleen reached the brim of the pelvis. I am going to put first on my list that this patient had Felty's syndrome, and I am going to put next, lymphoma, with the third possibility, monocytic leukemia.

DR. DANIEL S. ELLIS: Did you consider the possibility of amyloidosis?

DR. GRAHAM: I should have considered that out loud. I did consider it, but the Congo-red test seemed to be normal and I though that ruled it out.

DR. BERNARD M. JACOBSON: Would you consider sarcoid?

DR. GRAHAM: An enlarged spleen can be found in sarcoid but I do not see much else to go with it. I do not think these bone changes fit with sarcoid.

DR. JACOBSON: You said earlier that you did not think the leukopenia was marked enough to be consistent with Doan's hypersplenism. Now you say it is consistent with Felty's syndrome.

*Case Records of the Massachusetts General Hospital (Case 32391). *New Eng. J. Med.* 235:490-493, 1946.

DR. GRAHAM: I did not realize that the leukopenia in Felty's syndrome had to be very marked. As a matter of fact one figure was given with a suggestion that the white-cell count seemed to be rather low, so that we do not know what the leukopenia actually was. I gather it was not a strikingly low count, however. I admit that there are inconsistencies in my position, but it is an inconsistent problem.

DR. LEWIS KANE: Do not certain cases of amyloid disease have a negative Congo-red test?

DR. ELLIS: Yes.

DR. MARIAN ROPES: It has been our experience that patients with so-called Felty's syndrome have turned out to have splenic enlargement on a basis other than just rheumatoid arthritis. In addition, I think the degree of abnormality of the liver function would be greater than we have seen although there are slight abnormalities of liver-function tests associated with rheumatoid arthritis. Also, such marked splenic enlargement as part of the rheumatoid arthritis would seem unlikely.

DR. F. DENNETTE ADAMS: While this patient was being studied in the hospital, we believed that she had two diseases, or perhaps three, not one. There was no doubt about the presence of mitral disease, with predominating stenosis. Before we had completed any tests at all, I was most suspicious of either sarcoid or Gaucher's disease. The latter was ruled out by the x-ray and bone-marrow studies. The x-ray appearance of the joints seemed most consistent with rheumatoid arthritis. My belief was that the most likely cause of the enlarged spleen was sarcoid. It was for this reason that I thought she should be surgically explored.

DR. JACOBSON: For the sake of the record, I think it should be mentioned that this abstract omits a few items. The patient had a few small lymph nodes on the left side of the neck. She had a positive tourniquet test. One temperature is given in the record, but actually she ran an intermittent low-grade fever throughout the hospital stay.

CLINICAL DIAGNOSIS

? Sarcoid disease of spleen.

DR. GRAHAM'S DIAGNOSIS

Felty's syndrome.
? Lymphoma.
? Monocytic leukemia.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, giant-follicle type, of liver (and spleen).

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The operation was a liver punch biopsy. The portal islands were markedly increased in size because of infiltration with mononuclear cells. These were evidently of the lymphocyte series, and in several areas they were arranged in the pattern of lymphoid germinal centers. There was considerable infiltration of the liver parenchyma as well. We believe that a diagnosis of malignant lymphoma was justified — probably of the giant-follicle type. This type is frequently associated with an enormous spleen, the so-called Brill–Symmers disease.

I think the eventual course of the patient confirms that diagnosis. She was given x-ray treatment, and, with as little as 300 r, the spleen shrank very markedly and by the time she had 600 r it was decided that she did not need any further treatment for the present.

DR. ADAMS: May I add one word, Dr. Mallory? We had previously discussed liver biopsy or spleen biopsy, but I was of the opinion that surgical exploration was advisable. It was Dr. Linton, whom I asked to explore her, who requested the liver biopsy prior to exploration.

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BRAVE NEW WORLD

WITH Congress broadening the scope of American technical assistance to overseas health projects, the demand for expert health personnel to participate in specific programs is rapidly increasing. Such programs are undertaken by the Federal Security Agency with high hopes and brave words: "we have learned that if our desire for peace is to triumph we must help all peace-loving people to conquer misery and disease."

The formula, then, is to find a peace-loving people in an underdeveloped area where poverty holds the populace in bondage, and disease is the cause of poverty. According to the "Fact Sheet" released by the Federal Security Agency, on March 23, 1950, "the economic development of these under-privileged areas may well be the key to world prosperity and world peace. And the key to economic development is the elimination of the critical health problems which in many areas make economic advancement impossible." Turn the key and presto! the gate opens on the threshold to Elysian fields of peace, prosperity and a democratic way of life. Wishful thinking is not a new pastime, but, in John Bunyan's time at least, a pilgrim's progress was recognized as beset with obstacles that today are missing from the propaganda sheets of modern visionaries. The hard facts are that the ecologic balance of any nation not only is a matter of "health and prosperity" and professed peace-lovingness but also has to do with numbers, geography, climate, trade, food supply, government, education and beliefs.

Earlier in this century, long before Mr. Oscar Ewing developed the gifts of prophecy and second sight, the United States Public Health Service performed a splendid job of disease control in Puerto Rico. The result is that the island, of approximately the size of Connecticut, which started with a population of perhaps 100,000 in 1800, now numbers over 2,000,000 inhabitants, who have been given the "means to eradicate many of the diseases which for centuries have held man in bondage."[1] From this noble and worthwhile accomplishment has come the lesson that problems of human misery, unemployment, overpopulation and housing shortages cannot be satisfactorily solved merely by sanitary measures, mosquito control, mass inoculations and the migration of population surpluses to New York City. Puerto Rico remains as the best example of a half-completed experiment where good intentions and good public health substitute for an all-out program designed to solve a pressing human problem. Meanwhile, the Federal Security Agency stands ready to try the same half-finished experiment in the other underdeveloped areas of the world inhabited by peace-loving peoples. Liberation from disease without preparation for a balanced ecology within the domain of a people's environment may just as well be the key to overpopulation, unemployment, communism and war as to peace, prosperity and perfection.

To deplore the misuse of easy phrases that roll like music off the tongue is not to advocate defeatism or to disparage conscientious efforts made for the improvement of backward peoples, wherever they

may be. May the recruiting program of the Federal Security Agency prosper, but may the vision of the pilgrim who accepts the call be broader than that of Johnny Appleseed! A beneficent impulse to prevent disease instead of planting apples is not enough in the second half of the twentieth century. To eliminate disease as one of the natural checks and balances on a nation's population is to be confronted with other checks, such as famine, lack of *Lebensraum* and war, forces exploited by Hitler and Mussolini. Man has already opened Pandora's box and found that the nucleus of the atom lies within. He still has the lid of the box open when he releases all the mechanisms that limit the increase of human populations, without anticipating and preparing for the consequences of his own good intentions. Good public health is more than the absence of disease. It is a part of good ecology.

EXPLORATORY THORACOTOMY

ELSEWHERE in this issue of the *Journal* Kaunitz calls attention to the need for exploratory thoracotomy in certain patients suspected of having carcinoma of the lung in whom bronchoscopy is negative. Many lesions in the periphery of the lung cannot be seen by bronchoscopy, and in some of them a positive cytologic diagnosis is not obtained by examination of the sputum or study of the washings obtained at the time of bronchoscopy. Exploratory thoracotomy is now no more of a procedure than exploratory laparotomy, and should be performed in good-risk patients suspected of having cancer.

One should, however, sound a note of warning against injudicious exploratory thoracotomy. In Kaunitz's Case 4, a sixty-five-year-old man, a pneumonectomy was done for organizing pneumonia. Fortunately, the patient recovered, but he has needlessly lost an entire lung. In another series, however, a patient who obtained a free chest survey film had a negative bronchoscopy, was operated upon as a cancer suspect and died. He had had no symptoms, and, in fact, he did not have cancer. A few such tragedies will undo much of the good being done by routine chest survey films. It should be remembered that patients and not their x-ray shadows are being operated on. The judgment of the physician or surgeon must be especially well considered when he is deciding whether or not to operate upon an asymptomatic patient with a negative bronchoscopy and negative cytologic studies.

PRESCRIPTION FOR GOOD WILL

PHYSICIANS seldom realize the ill will needlessly engendered because of misunderstandings of the regulations that govern the prescription and sale of certain drugs. Pharmacists have been more keenly aware of the situation. When the representatives of the Massachusetts State Pharmaceutical Association met with the committee appointed at their request by the Massachusetts Medical Society, this was one of the first matters brought up for consideration.

If a patient asking a druggist for a refill of a prescription is informed that he cannot be given it unless he obtains a new prescription from his doctor, he may feel provoked by what seems to be red tape, or he may even suspect collusion between the druggist and physician to make more money out of his case. A busy doctor receiving telephone calls from the druggist about such prescriptions may exhibit irritation, failing to realize that the druggist is acting in the interest of both patient and physician. A physician may object when he finds that the druggist has attached to a bottle of phenobarbital tablets prescribed for an anxious, nervous patient a label reading "warning, may be habit-forming," not realizing that the druggist is obliged by law to use this label when he dispenses such medication except when the prescription carries the letters "N.R." or other indication that it must not be refilled.

Every physician should be familiar with the laws discussed in the Notes from the Medical Examiner elsewhere in this issue of the *Journal*. For the sake of clarity, he should, when prescribing "dangerous drugs," indicate his instructions to the pharmacist by writing "N.R." (not to be refilled) or "refill as needed for . . . months." He should also explain the instructions to the patient. Attention to these matters should prevent ill will and misunderstandings between physicians and pharmacists, and between both professions and the public.

WESTWARD HO!

HEEDING the advice usually attributed to Horace Greeley and already acknowledged as such in these columns,* two members of the editorial board of the *Journal* have succumbed to an insupportable pressure from without and will this summer turn their footsteps westward.

West, to the sophisticated post-war Bostonian, no longer refers to the trackless wilderness beyond Worcester, Massachusetts, but to that part of this vast continent that lies even beyond the great barrier of the the Allegheny Mountains.

To these transappalachian regions Editors Carroll B. Larson and Charles H. Burnett will wend their separate ways, Dr. Larson to become professor of orthopedic surgery at the University of Iowa; Dr. Burnett to assume the post of professor and head of the Department of Medicine at Southwestern Medical College, in Dallas.

The *Journal* congratulates the schools that have acquired these two able members of its board. While it regrets the personal loss it sustains in their departure, it also takes satisfaction in the feeling of having sent its personal envoys into other scientific and cultural centers. Even as they sing their new songs in these strange lands, it is not impossible that the young professors may also continue some sort of liaison with sedate New England, old, but still willing to learn.

*Editorial. Young man, go west. *New Eng. J. Med.* 241:628, 1949.

The Water Cure Journal, published by the Messrs. Fowler & Co., New York, has just entered upon its tenth volume. The picture upon the title page is very significant, and must please those who delight to play *in the water.*

Boston M. & S. J., *July 10, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

AYER — Silas H. Ayer, M.D., of Boston, died on June 15. He was in his eighty-ninth year.

Dr. Ayer received his degree from Harvard Medical School in 1884. Four sons survive.

LUND — Fred B. Lund, M.D., of Newton, died on June 22. He was in his eighty-sixth year.

Dr. Lund received his degree from Harvard Medical School in 1892. He was formerly lecturer on anatomy at Harvard Medical School and surgeon-in-chief at the Boston City and Carney hospitals and a member of the surgical staff of the Massachusetts General Hospital. He was a former president of the Society of Clinical Surgery, a member of the American Surgical Association and New England Surgical Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, four sons, a daughter and twelve grandchildren survive.

BOSTON MEDICAL LIBRARY

VARIA

The annual convention of the Medical Library Association, held in Boston during the week of June 19, with the Boston Medical Library as principal host, had the largest attendance ever recorded at a meeting of the Association. The number registered was 260. There were a number of distinguished guests from foreign countries, including Canada, England, India and South America. The meeting was very successful as evidenced by the continuous enthusiasm of the members assembled from all parts of the country.

AWARD TO THE DIRECTOR

During the recent convention of the Medical Library Association, an international organization, held in Boston, the week of June 19-24, an outstanding honor was conferred on James F. Ballard, director of the Boston Medical Library. He was certified a "medical librarian" and was given the number two certificate in honor of his long career in medical library work and his work for the Association over a period of many years. The project for voluntary certification of medical librarians was initiated in 1947 at the Cleveland meeting and was finally approved by the Association at the Galveston meeting in 1949. Miss Mary Louise Marshall, of New Orleans, who at that time was chairman of the Committee on Standards for Medical Librarianship, expressed the desire to be granted the number one certificate. Her work on the Committee has now been rewarded, and Miss Marshall and Mr. Ballard at the present time hold the only certificates granted by the Association.

Mr. Ballard has been connected continuously with the Boston Medical Library for fifty-seven

years. On October 24, 1892, he entered its service as errand boy, and in 1909 he was appointed assistant librarian, the highest paid position in the Library and equivalent to the present title of director; the title was changed in 1927 since it seemed more fitting to the position.

In 1942, in honor of the completion of fifty years of service, at a reception and tea in the Library, a life-sized head-and-shoulders plaque, sculptured by Mrs. Doris Appel, was unveiled. Likewise, the Ballard Revolving Publication Fund was established.

Mr. Ballard has been actively interested in library affairs for many years. He is ex-president of the Medical Library Association, serving during 1937 and 1938, and ex-chairman of the Boston Chapter and the national Biological Sciences Group of the Special Libraries Association. He was chairman of the Trustees of the Massachusetts State Library from 1935 to 1941, and at present is a trustee of the Milton Public Library, consulting librarian to the Boston City Hospital and the Tufts College Medical School and a charter member of the Board of Consultants of the Army Medical Library at Washington, where he holds the position of special consultant. He is the author of the modern classification of the Boston Medical Library, now in its third edition, 1946, 1948, used in a large number of medical libraries throughout the world. It has been translated into Japanese, and at present is being rendered into Spanish. He has also written two books, *A Catalogue of the Medical Incunabula Contained in the William Norton Bullard Loan Collection* (Boston: privately printed, 1929) and *A Catalogue of the Medieval and Renaissance Manuscripts, and Incunabula in the Boston Medical Library* (Boston: privately printed, 1944). A second volume of this catalogue is now in the press, bringing the acquisitions of this class of material down to date. He has written a large number of professional papers and has been a reviewer for the *New England Journal of Medicine* for the past seven years and has written a very large number of notes and reviews during this period. Mr. Ballard is considered an authority on early medical literature. He is a charter member of the Boston Medical History Club and has served as secretary or curator since its organization in 1921. From time to time he has surveyed medical libraries throughout the United States and has appraised the libraries of deceased physicians. During 1920, he went abroad for the China Board of the Rockefeller Foundation to purchase a medical library for the Peking Medical School. During his trip abroad he also acted for the Harvard Medical School and the Army Medical Library. Upon his return he was commissioned to establish a medical library for the new University of Rochester School of Medicine by the General Education Board.

NOTES FROM THE MEDICAL EXAMINER*

PRESCRIPTION OF BARBITURATES AND OTHER DANGEROUS DRUGS

A great deal of confusion exists among both physicians and pharmacists in Massachusetts regarding the refilling of prescriptions of the so-called "dangerous drugs." This is partly the result of conflict between state and federal laws concerning the retail sale of drugs. The Federal Food, Drug and Cosmetic Law restricts the refilling of prescriptions for: all dangerous drugs of any kind, including barbiturate preparations, regardless of the amount of barbiturate involved; and all packages and preparations that contain the printed legend "to be dispensed only by or upon the prescription of a physician" or similar language (this includes a great host of drugs in addition to the sulfonamides and antibiotics). The pharmacist is prohibited from refilling such prescriptions unless the physician actually stipulates that they may be refilled and also states the limits of time during which this may be done. Official interpretation of the federal law indicates that the refilling of a prescription that has not been allowed in writing by the physician is illegal. Actually, the refilling of such prescriptions defeats the purpose of the federal legislation by allowing on the one hand self-medication and on the other the improper dispensing by the pharmacist of dangerous drugs.

The basis of the confusion arises out of the Massachusetts law, Sec. 3, Chap. 598 of the Acts of 1948, which provides that no retail druggist may sell hypnotic or somnifacient drugs or any dangerous drugs except upon the written prescription of a physician, dentist or veterinarian. A prescription for such drugs may be refilled if the prescription does *not* bear any indication that it is not to be renewed or refilled. If the physician marks the prescription "N.R." or not to be repeated, such a prescription cannot be refilled under any circumstances. "Dangerous" or "harmful" drugs, for the purposes of the laws of the Commonwealth of Massachusetts, include any of the following drugs and any derivatives or active principles, preparations, compounds or mixtures thereof having similar harmful action: amidopyrine, amphetamine (Benzedrine), — except those preparations for nasal or other external use, — desoxyephedrine, cantharides, — except for external use in combination with other ingredients unfit for internal administration, — barbituric acid, chloralhydrate, paraldehyde, thyroid, pituitary, oil of croton, oil of pennyroyal, oil of savind and oil of tansy.

Thus, it appears that to avoid confusion a physician should *always* specifically indicate his desires regarding the refilling of prescriptions of somni-

*Presented by the Department of Legal Medicine, Harvard Medical School.

facient and other dangerous drugs either by indicating that certain prescriptions may be refilled during stated periods or that they may not (N.R.). If no notation to this effect is made upon the prescription, under the interpretation of the federal law it may not be renewed, whereas the phraseology of the Massachusetts regulatory statute in a directly opposite manner allows such renewal.

Aside from the strictly legal aspects of this problem, two kinds of death, neither of which is uncommon, warrant further evaluation of barbiturate-prescription practice on the part of physicians. The first is that easy availability of sleeping powders renders the use of such drugs one of the commonest methods of suicide. A physician may unwittingly provide a depressed person with an adequate suicidal dose by the overprescription of barbiturate. Whereas a dozen capsules would have been sufficient for a particular course of sedation therapy, 24 or 36 capsules are ordered. Though persons intending to commit suicide contrive to hoard capsules or obtain them through other channels, a certain number would be deprived of an easily available exit by cautious prescription. Some of these perhaps might then survive the throes of a severe depression or anxiety state.

The second point is accidental poisoning with somnifacient drugs, particularly the barbiturate compounds. Some of these are truly preventable accidents. If a container of barbiturate is allowed at the bedside, a partially sedated patient, having already taken one or two capsules, may manifest sufficient depression of the higher centers as to treble or quadruple therapeutic doses in an attempt to induce sleep and thereby succeed in poisoning himself. Another group of accidental poisonings, perhaps requiring more emphasis, includes deaths of alcoholic persons sedated with barbiturate. A remarkable synergism between alcohol and barbiturate compounds exists. Relatively small doses of barbiturates, when taken with quantities of alcohol not ordinarily fatal, may cause fatal poisoning. Each year several investigations including autopsy examination performed by medical examiners in Massachusetts reveal this combination of circumstances. Judicious prescription and proper instruction of patients should aid in the prevention of this type of poisoning.

MICHAEL A. LUONGO, M.D.

Instructor in Legal Medicine, Harvard Medical School, and *Associate Medical Examiner*, Suffolk County.

MISCELLANY

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

At the fourth annual meeting of the American Electroencephalographic Society on June 10 and 11 in Atlantic City, New Jersey, the following officers were elected for the ensuing year: president, Robert S. Schwab, M.D., Massachusetts General Hospital, Boston; vice-president, James L. O'Leary, M.D., Washington University School of Medicine, St. Louis, Missouri; treasurer, Mary A. B. Brazier, Ph.D., Massachusetts General Hospital, Boston; and secretary, John A. Abbott, M.D., Massachusetts General Hospital, Boston. Charles E. Henry, Ph.D., Institute of Living, Hartford, Connecticut, was elected to the Council.

AMERICAN HEART ASSOCIATION

Dr. Howard B. Sprague, of Brookline, was recently elected president of the American Heart Association at its twenty-sixth annual meeting in San Francisco. Dr. Sprague is a former president of the Massachusetts Heart Association.

Dr. Paul D. White, of Boston, a former president of both the American and the Massachusetts Heart associations, was one of six recipients of the Gold Heart Awards presented to four surviving signers of the original articles of incorporation of the American Heart Association and to two laymen for outstanding service in obtaining public support for the Heart Campaign.

CORRESPONDENCE

EARLY TONSILLECTOMY

To the Editor: Readers of the *Journal* may be interested in the following excerpt from a letter written by my great-uncle Samuel, late of Denver, Colorado, which was published in the Manchester (Massachusetts) *Cricket*, on February 20, 1904:

> It is 50 years ago since I left home for Boston and entered the office of . . . to learn to be a doctor. He was a specialist on throats; for any case of sore throat he cut out the tonsils. I shall never forget the poor devil who came to him from Maine, who, after his tonsils were cut out, insisted on the doctor's cutting his head off and finishing the job. The poor fellow bled so bad he came near choking to death. For consumptives he would load them up with cod liver oil and quack medicine, which I bottled up in the cellar and he charged $1 a bottle.

Perhaps "public relations" nearly a hundred years later are not as poor as some people think. At least they seem to have improved in the last fifty years!

HARRIET P. LEACH, M.D.

Lowell, Massachusetts

BOOK REVIEWS

The Captains and the Kings Depart: and other stories. By Helen Eustis. 8°, cloth, 230 pp. New York: Harper and Brothers, 1949. $2.75.

This volume consists of a group of short stories in which the author has presented in a clear, realistic fashion living characters in whom are expressed psychodynamic mechanisms. She has succeeded in portraying them in such a manner that the reader is immediately aware of the underlying personality difficulties and struggles. She has combined with suspenseful writing an able portrayal of the development of personality in its various facets by choosing in each of her stories persons whose past and present reveal factors that are operative in the behavior and thinking of most people but ordinarily lie beyond the view of the casual observer.

In short, the author presents a group of interesting, readable, stimulating stories in which the primary portrayal of her characters is immediately evident and striking.

Modern Practice in Anesthesia 1949. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A. 8°, cloth, 606 pp., with 227 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. $12.50.

As editor, Dr. Evans has compiled a book of 38 chapters written by 25 authors. Of these contributors 2 are pathologists, 2 surgeons, 1 an anatomist, and 1 a cardiologist, and the remainder are anesthesiologists.

The field of anesthesiology is covered rather comprehensively. The scope of the specialty is made evident by a

glance at the table of contents. It is at once apparent that this book is directed toward the clinician rather than the laboratory investigator. The basic sciences receive relatively less emphasis than practice in the operating room.

Most of the chapters tend to be brief, and to avoid exhaustive discussions of their particular subjects. This might be the chief criticism of the book. Yet a complete survey of each topic would fill many volumes. This work probably contains as much information as could be compressed conveniently between two covers.

Both the old, established procedures in anesthesia and the more recent advances are discussed. A proper balance is maintained between the two. The authors do not fall into the error of scrapping older technics and agents for newer ones on the fallacious premise that a change is necessarily an improvement. In this regard Dr. Gould, quoting Challis (1947), says that "The consumption of ether in the average London teaching hospital has shown no tendency to fall in recent years, and averages half to three-quarters of a ton per annum. This fact may help to disillusion those ultra-modernists who believe that cyclopropane, thiopentone and curare are the last words in anesthesia."

The chapters may be divided into a half-dozen different groups, as follows: general considerations (13 chapters dealing with history, the basic sciences, signs of anesthesia, pre-operative and postoperative care, posture and emergencies in anesthesia); technics in anesthesia (7 chapters); supportive therapy (3 chapters dealing with fluid and oxygen therapy and shock); age extremes (pediatric and geriatric anesthesia, discussed in 2 rather brief chapters); modifications in technic demanded by the type of surgery — for example, thoracic and dental surgery (10 chapters); and modifications in technic demanded by certain complicating diseases — namely, diabetes mellitus, asthma and heart disease (3 chapters).

The style and content of well over a dozen chapters render them worthy of special attention. Of these the reviewer was particularly impressed by works of Galley and Gould. Dr. Galley's discussion of complications associated with respiration and circulation in his "Anaesthetic Emergencies" is of the first order. "Anaesthesia and Analgesia in Dental Surgery" is an excellent chapter written by Dr. Gould.

This book is very readable throughout, and nowhere are fundamentals obscured by minutiae or meandering. The quality of paper, printing and binding is good.

Variations in concepts and procedures of anesthesiology between Great Britain on the one hand and Canada and the United States on the other should be of interest to practitioners on this side of the Atlantic.

The Biology of Mental Defect. By Lionel S. Penrose, M. A., M.D. With a preface by Professor J. B. S. Haldane, F.R.S. 8°, cloth, 286 pp., with 10 figures, 47 tables and 7 plates. New York: Grune and Stratton, 1949. $4.75.

The author in his foreword states that the purpose of this book is to discuss mental deficiency from the point of view of human biology. Bearing this in mind, one will find that the book gives a remarkably thorough and yet not too extensive presentation of this aspect of mental defect. One must not expect a review of clinical material and practice, but many points of clinical interest are touched upon, so that the reviewer found the book of value clinically as well as theoretically. Much of the new work on the genetics of mental defect is given from the author's point of view, and other causes are touched upon briefly in passing so that this book should be used to supplement other reading and thus a rounded picture of the general field may be obtained.

There is an excellent chapter on problems of causation and also one on methods of analysis; both are outstanding. All in all, this book should be considered essential for anyone with even a mild interest in this field.

Acute Appendicitis and Its Complications. By Frederick F. Boyce, M.D. 8°, cloth, 487 pp., with 81 illustrations. New York: Oxford University Press, 1949. $8.75.

As stated in the preface, this book is written from the point of view that acute appendicitis is an inherently serious, extremely urgent, potentially deadly disease and, furthermore, that early diagnosis, prompt operation and abstinence from purgation in simple acute appendicitis may be less dramatic than cure of appendiceal peritonitis by chemotherapy but they will save more lives in the long run. This theme is well emphasized throughout the volume.

One finds here for the first time a book solely devoted to the appendix and its diseases. The author interestingly presents the historical background of appendicitis. This is followed by an adequate discussion of the embryology, anatomy and physiology of the appendix. The chapters on the etiology and bacteriology of appendicitis are complete. In dealing with the clinical picture and diagnosis one finds a more thorough discussion than in the usual textbooks of surgery. The section on surgical technic offers little that is not found elsewhere. The complications of appendicitis are well covered. The over-all value of this book is great. It should be of particular value to the young man entering surgery who has not personally met the many manifestations of this disease. The owner of this book will have at his command an easily readable reference work on the commonest of all surgical abdominal diseases, appendicitis.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Malariology: A comprehensive survey of all aspects of this group of diseases from a global standpoint. In 2 volumes. By sixty-five contributors. Edited by Mark F. Boyd, M.D., M.S., M.P.H. 4°, cloth. Vol. I, 787 pp., with 237 illustrations and 127 tables; Vol. II, 855 pp., with 198 illustrations and 53 tables. Philadelphia: W. B. Saunders Company, 1949. $35.00 for the set.

This comprehensive treatise on malaria covers all aspects of the disease and associated conditions. The material is divided into five sections: history, parasitology, definitive hosts, intermediate host and control and eradication. The various chapters are documented with bibliographies. There are extensive indexes of authors and subjects. The publishing is excellent, and the work is recommended to all medical libraries and to all persons interested in the subject.

Physiology of the Nervous System. By John F. Fulton, O.B.E., M.D., D.Sc., LL.D., Sterling Professor of Physiology, Yale University School of Medicine. Third edition, revised. 8°, cloth, 667 pp., with 140 illustrations. New York: Oxford University Press, 1949. $10.00.

In this third edition of a standard work, the author has brought his text up to date since the publication of the previous edition in 1943. Much material, including the operation of frontal lobotomy for the relief of abnormal mental states, has been added on neurophysiology. A comprehensive bibliography is appended to the text, and there is a good index. The publishing is excellent, and the book is recommended to all medical libraries and to all persons interested in the subject.

The Arthropathies: A handbook of roentgen diagnosis. By Alfred A. deLorimier, M.D., radiologist, St. Francis Hospital, San Francisco, and consultant in radiology for the United States Army at Letterman General Hospital. Second edition. 8°, cloth, 335 pp., with 157 plates. Chicago: Year Book Publishers, Incorporated, 1949. $7.00.

This handbook has been revised and brought up to date since the publication of the first edition in 1943. The author has taken advantage of the opportunity to provide new reproductions superior to the original pictures. Also, descriptions have been furnished for each entity. A bibliography of selected references has been appended to the text, and there is a good index. The volume is well published and should prove of value to roentgenologists and to all persons who are interested in the subject.

(*Notices on page xi*)